IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

GW Office of Continuing Education in the Health Professions

27th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

VOLUME 1

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

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

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Agenda Day 1: Saturday, August 20, 2022

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

Agenda Day 2: Sunday, August 21, 2022

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

Agenda Day 3: Monday, August 22, 2022

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

Agenda Day 4: Tuesday, August 23, 2022

AM Moderator: Roy Gulick, MD					
#	**Start**		**End**	**Presentation**	**Faculty**
QP4	**8:30 AM EDT**	**-**	**9:00 AM EDT**	**Daily Question Preview Day 4**	**Roy Gulick, MD**
34	9:00-AM	-	9:30 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
35	9:30 AM	-	10:15 AM	HIV Associated Opportunistic Infections I	Henry Masur, MD
36	10:15 AM	-	10:30 AM	HIV Diagnosis	Frank Maldarelli, MD
37	10:30 AM	-	11:15 AM	Antiretroviral Therapy	Roy Gulick, MD
38	11:15 AM	-	11:30 AM	HIV Drug Resistance	Michael Saag, MD
39	11:30 AM	-	12:15 PM	Antiretroviral Therapy for Special Populations	Roy Gulick, MD
	12:15 PM	-	1:00 PM	Lunch Break	
BR4	**1:00 PM**	**-**	**2:00 PM**	**Board Review Day 4**	**Drs. Gulick (Moderator), Bennett, Bloch, Dorman, Maldarelli, Pavia, and Saag**
PM Moderator: Andy Pavia, MD					
40	2:00 PM	-	2:45 PM	Syndromes that Masquerade as Infections	Karen Bloch, MD
41	2:45 PM	-	3:30 PM	Tuberculosis in Immunocompetent and Immunosuppressed Hosts	Susan Dorman, MD
42	3:30 PM	-	4:15 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
FC8	**4:15 PM**	**-**	**4:45 PM**	**Faculty Q&A**	**Drs. Gulick (Moderator), Block, Dorman, Dupont, Maldarelli, and Saag**
43	4:45 PM	-	5:45 PM	Respiratory Viral Infections Including Influenza, Immunocompetent, and Immunocompromised Patients	Andy Pavia, MD
44	5:45 PM	-	6:00 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
45	6:00 PM	-	6:30 PM	Core Concepts: Antiviral Drugs	Andy Pavia, MD
FC9	**6:30 PM**	**-**	**7:00 PM**	**End of the Day Meet the Professor (Live Registrants Only)**	**Drs. Bloch, Gulick, Dorman, Maldarelli, Pavia and Saag**

Agenda Day 5: Wednesday, August 24, 2022

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

Online Only Lectures

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

Primers and Study Guides

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

Board Review Question Sets

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

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COURSE OVERVIEW

ABOUT THE COURSE

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

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

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

EDUCATIONAL OBJECTIVES

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

PROGRAM FACILITATORS

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ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

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

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

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

LIVE COURSE

Accreditation

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

CME Credit for Physicians

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

Claiming MOC Points

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

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

Deadline for Claiming MOC Points

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

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

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

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

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

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

ONLINE MATERIALS

Credit

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

MOC Points

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

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

Claiming Credit and MOC

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

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

Deadlines for Claiming MOC Points

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

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

OVERVIEW OF ONLINE MATERIALS AND INSTRUCTIONS FOR CLAIMING CREDIT AND MOC

Online Only Lectures	**CME Hours: 9**	**MOC Points: 9**
• These lectures feature topics that were not covered in the live course.		
Board Prep Questions	**CME Hours: 53**	**MOC Points: 53**
• There are four (4) sets of 100 board prep questions. • There are one (1) set of 100 photo opportunity questions. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
Online Primers and Study Guides	**CME Hours: 12**	**MOC Points: 12**
• There are eight (8) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

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

Current Access

Instructions for accessing the Online Materials

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

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

Important Links

Please note that you must be logged in to access.

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

FACULTY LISTING

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

FACULTY DISCLOSURES AND RESOLUTIONS

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

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

PLANNERS

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

Both planners also resolved financial disclosures

STAFF

- Leticia Hall
- Naomi Loughlin
- Sheena P. King

The following faculty members (speakers) disclosed commercial relationships:

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

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

Agenda Day 1: Saturday, August 20, 2022

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

01

Introduction

Drs. Bennett and Masur

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Introduction

Henry Masur MD
Jack Bennett MD

6/21/2022

This Is Board Review

- **This is Board Review**
  - …not meant to be "What's New"
  - This may not mimic your practice but
    - Hopefully it will mimic exam
    - Faculty provides their *"best guess"* about the information and type of questions likely to be on the certification, recertification, and check-in 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!!!

Video, Audio, On Line Materials

- **All Materials Are Available On Website until December 2023**
  - Syllabus
    - Current lectures will be replaced on e-version with the slides "as presented"
      - (in case there are minor changes or answers included that were absent from syllabus)
  - Corrections, answers to daily questions and other material will be added daily to the website during course and later as appropriate

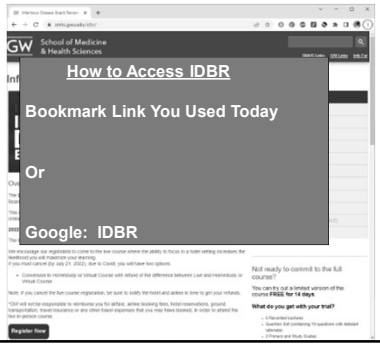
Components of the Hybrid Course

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

Components of the Hybrid Course

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

– Comparison to group metrics

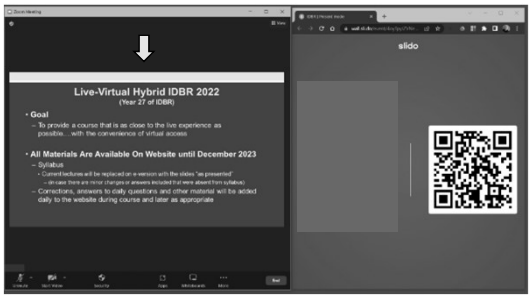


01 – Introduction

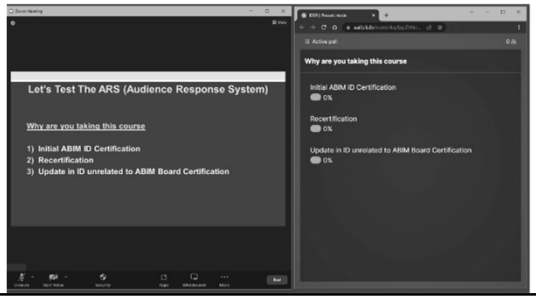
Speaker: John Bennett, MD and Henry Masur, MD

- Sign in to Slido with a user name likely to be unique
- Use the exact same name every day, i.e., spelling + caps
- Can be a pseudonym

You Need One Window for Zoom and Second Window For Slido



Zoom / Slido Polling



End of the Day Meet Professor

- **Only available to Live Participants**
- **Faculty will be at designated locations announced at end of day**

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

IDBR APP

- **Download the IDBR App from Apple store or Google Play store**
  - Download Eventscribe
  - Search for course by entering "2022IDBR"
  - Log in with the email and password that was emailed to you
  - Problems: email idbr@gwu.edu or call (202) 994-4285
- **You can use this app during the course, or until 12/2023, on your cell phone or tablet to look at the syllabus**

Which Will You Be?

How to Get The Most Out of Virtual Course

- **This is a long course and it's (obviously) virtual**
  - Decide how you learn best over 10+ hours x 5 days
  - If you don't/can't watch the lectures consecutively…they are all archived
- **Use the ARS System**
  - To stay awake, be engaged and competitive!
  - Answer the questions and see how you compare to your peers

IDBR Program for Certification/Recertification Preparation

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

- **Live/Virtual course for 5.0 days**
  - **Live Board Review Questions**
  - **Rationales and daily scores published online by your ID at end of each day**
- **Online Board Review Type Questions**
  - **400 Online questions with rationales**
- **Online Primers (Tables or Charts or Photos)**
  - **Clinical Microbiology**
  - **Resistance: Antibacterial, Antifungal, Antiviral, HIV**
  - **Skin Ulcers**
  - **Rickettsia**
  - **115 "Images You Should Know" – rapid pre-exam review**
- **Online Recordings of 2022 Lectures (posted within a few days-2 weeks after course)**
  - **Listen to audio by MP3 (download and transfer to any device)**
  - **Watch slides while listening to synchronized audio**
- **Online Only Lectures**
  - **Talks we wished we had time for during these 5.0 virtual days**
  - **Equally important as live lectures**

Accessing The Course

- **Problems accessing lectures or chat room?**
  - **Telephone help line: (202) 994-4285**
  - **Email help hotline: idbr@gwu.edu**
  - **Naomi Loughlin**
    - **nbl7396@gwu.edu**
    - **(571) 385-5550 (cell)**
    - **(202) 994-4509 (office)**
- **Faculty welcome your questions**
  - **Send email to idbr@gwu.edu or use q and a feature**

CME and MOC

Total Possible: 114 CME and 114 MOC

- **CME**
  - **You must fill out lecture evaluations (via IDBR website)**
  - **You must request CME (via IDBR website)**
  - No pre-test or post-test
  - Total possible hours - 114
    - Lectures – 43
    - Enduring Material 58 (online IDBR website)
- **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)

01 – Introduction

Speaker: John Bennett, MD and Henry Masur, MD

IDBR Directors and Co-Directors



Richard Whitley
University of Alabama


Andy Pavia
University of Utah


Kieren Marr
Johns Hopkins


Trip Gulick
Weill Cornell


Paul Auwaerter
Johns Hopkins


David Gilbert
University of Oregon

Behind Scenes Staff


Leticia Hall-Salam
IDBR Program Director


Sheena P. King
CE Coordinator


Naomi Loughlin
IDBR Program Coordinator


Mike D'Anthony
Recording


Mark LaBue
AV Director

Advice from Jack Bennett MD

Let's Test the ARS (Audience Response System)

Why are you taking this course

1) **Initial ABIM ID Certification**
2) **Recertification**
3) **Update in ID unrelated to ABIM Board Certification**

Question 2

Where do you work

1) **East coast, United States**
2) **Midwest, United States**
3) **South, United States**
4) **West coast, United States**
5) **Europe**
6) **Asia**
7) **Other**

Question 3

Which parts of IDBR on line materials have you looked at prior to the course

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

Let's Begin!

The End

02

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

Dr. Helen Boucher

02 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

How to Prepare for Certification and Re-Certification Exams

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

7/18/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)
- Treasurer, Infectious Diseases Society of America
- Member, ID Board, American Board of Internal Medicine

Website

www.abim.org

https://www.abim.org/~/media/ABIM%20Public/Files/pdf/exam-blueprints/certification/infectious-disease.pdf

3

Times are Changing at ABIM! Infectious Diseases Certification

- Initial Certification Exam – no change
- Maintenance of Certification is Changing - Options:
  - Every 10 year MOC exam
  - Every 2 year Knowledge Check-in (KCI)
    - Offered thru 2021 (but not offered in 2022)
  - New Ongoing Assessment: Longitudinal Knowledge Assessment (LKA) begins 2023 with 1 year waiver
- If you are due for MOC assessment in 2022, you can either take the 10 year MOC or take nothing and start the LKA in 2023

4

Certification Exams

- One day computer exam
- All questions: multiple choice, single best answer only
- Initial Certification:
  - Four 2-hour sessions: up to 60 questions each = 240
  - Time remaining for each session on computer screen
  - Message box will tell you when 5 minutes left in a session
  - Including registration, optional tutorial (up to 30 minutes), instructions, test, breaks ~ 10 hours.
- Maintenance of Certification (formerly recertification): Three 2-hour exam sessions ~ 8 hours or KCI
  - available through 2021

5

Knowledge Check-in (KCI) Exam

- Every 2 years
- Officially ends in 2022 but will not be offered after 2021
  - One year waiver will be offered for LKA
- Up to Date allowed (different environment so take the practice exam to become familiar)
- Home or Test Center
  - Special monitoring at home
    - Video camera must be on for the entire time
    - Desk must be clear, internet connection strong, etc.
    - Can be disqualified for irregularities (e.g., someone enters the room)

6

02 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

New Option: Longitudinal Knowledge Assessment (LKA)

Current Plan (subject to change):

- 5 year recertification period
- 30 questions emailed every 3 months
  - Don't need to answer all at one time; can spread out over the quarter
- Four minutes to answer online
  - Open book
  - Correct answer and rationale then provided
- Must answer 100 Q's per year (out of 120)
- Earn 0.2 MOC credits/correct answer
- After 5 years and at least 500 questions answered, ABIM provides pass/fail notification
- 500 correct answers fulfills required 100 MOC points

https://www.abim.org/lka/

7

ABIM COVID Updates for MOC

NO ONE WILL LOSE CERTIFICATION IF THEY AREN'T ABLE TO COMPLETE AN MOC REQUIREMENT THIS YEAR.

If you had an assessment, points or an attestation requirement due in 2020 or 2021, **you now have until the end of 2022 to complete it**.

If you are due for an assessment in 2020, 2021 or 2022, **you'll be able to participate in the** longitudinal assessment when it launches in your specialty (see the longitudinal availability and rollout schedule).

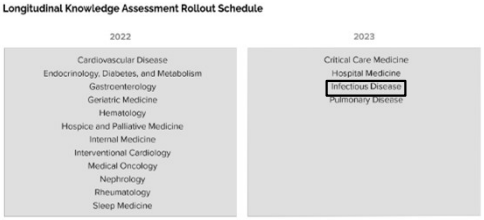
If you're among this group and certified in Critical Care Medicine, Hospital Medicine, Infectious Disease or Pulmonary Disease, you'll receive an additional year to take an assessment. This means you can wait until 2023 and choose from the traditional, 10-year MOC exam or longitudinal assessment at that time.

We will not be offering the Knowledge Check-In after 2021.

https://blog.abim.org/abim-to-extend-all-moc-requirement-deadlines-through-2022/

8

Longitudinal Knowledge Assessment (LKA)



https://blog.abim.org/abim-quarterly-news-note-spring-2021/

9

Exam

- Can change answer until 60 question section over. Note ones unsure of and review them at end of session
- Roughly 20% of questions don't count = new questions being pretested

10

Exam

- Little less than two minutes per question.
- Unanswered questions marked wrong, so guess if don't know
- Read the whole question!
- If question seems ambiguous, or seems to have two correct answers, you might be right. It may be a new question being tested for first time.
  Give your best answer and don't fret.

11

Breaks

- Breaks are optional. Take them!
- 3 breaks during day: total 100 minutes
- 1 break after each of first 3 test sessions.
- Can use some or all of break time.
- Amount of break time used after each session subtracted from total time.
  - For example: if take 10 minute break after session one, amount of break time remaining for exam is 90 minutes.
- 80 minutes break time for MOC exam (2 breaks).

12

02 – How to Prepare for Certification and Re-Certification Exams

Speaker: Helen Boucher, MD

Exam

- Confirmation email will specify appointment time and give driving directions to test center
- Check out site before exam:
  - Where is it? Where to park? Where to eat?
- Arrive ½ hour early
- Each testing center has 8 -25 workstations
- An administrator will be present
- At start of exam: see several screens reviewing instructions about taking exam, and asked to agree to a Pledge of Honesty

13

Exam

- You will need personal ID (2 types): government-issued ID with photo and signature (driver's license, passport, etc.)

  And

  another form of ID with signature or photo (Social Security card, credit card, ATM card, etc.)
- Not allowed to take exam with expired ID
- Palm vein scan, security wanding, signature and photograph will be taken

14

Exam

- Short orientation then taken to computer workstation
- May request left-handed mouse
- May request instructions adjust height and contrast of computer
- Erasable notepads provided and can type and save notes in pop-up box that accompanies each question
- Can request headphones or earplugs; cannot bring your own
- Any problem: Don't get up! Raise your hand
- Electronic fingerprint each time enter and exit testing room - allow 10 min to check back in

15

Disabled Test Takers

- ABIM complies with the Americans with Disabilities Act (ADA)
  - They will make reasonable modifications to exam procedures as necessary, but there are limits
- Each request individually evaluated
- For more info see Forms of Accommodation on ABIM website

16

Not allowed in test room (small storage locker provided)

- Electronic devices: cell phone, PDA, pager, beeper
- Calculator, calipers, camera
- Watch – clock is in testing room
- Wallet, purse
- Briefcase, backpack
- Jacket, coat (sweater OK)
- Books, scratch paper, pens, pencils (noteboards provided)
- Medications require prior approval (contact us feature on website)
- Food and drink
- (Bring drinks for breaks to keep in locker; can bring lunch, but no refrigeration)

17

Questions about exam day

- Call ABIM 1-800-441-ABIM (2246)

  Mon-Fri: 8:30AM – 8PM

  Saturday: 9AM – 12PM

18

Exam Tutorial

- **Examples of the exam question formats are available in a tutorial at the ABIM website:**
  - **https://www.abim.org/certification/exam-information/infectious-disease/exam-tutorial.aspx**

19

Exam Format

Exam is composed of multiple-choice questions with a single best answer, predominantly describing patient scenarios.

- **Questions ask about the work done (that is, tasks performed) by physicians in the course of practice: Making a diagnosis**
- **Ordering and interpreting results of tests**
- **Recommending treatment or other patient care**
- **Assessing risk, determining prognosis, and applying principles from epidemiologic studies**
- **Understanding the underlying pathophysiology of disease and basic science knowledge applicable to patient care**

20

- **>75% patient case presentations**
  - **not trying to trick you**
- **Normal lab values provided**
- **Pediatric questions not likely**
- **Very little basic science:**
  - **mechanisms of resistance - ESBL, KPC**
- **Very little clinical microbiology (occasional clues):**
  - **things you could do to help lab**
    - **e.g. oil on media for lipophilic yeast**
      Iron and 30° incubation for *M. haemophilum*

21

Exam Content

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

22

2019 ID Exam Blueprint

Medical Content Category	% of Exam
Bacterial Diseases	27%
Human Immunodeficiency Virus (HIV) Infection	15%
Antimicrobial Therapy	9%
Viral Diseases	7%
Travel and Tropical Medicine	5%
Fungi	5%
Immunocompromised Host (Non-HIV Infection)	5%
Vaccinations	4%
Infection Prevention and Control	5%
General Internal Medicine, Critical Care, and Surgery	18%
	100%

23

Clinical Syndromes

- Pleuropulmonary infections
- Infections of the head and neck
- Infections and other complications in HIV/AIDS
- Cardiovascular infections
- Central nervous system infections
- Gastrointestinal and intra-abdominal infections
- Liver and biliary tract infections
- Skin and soft tissue infections
- Bone and joint infections

24

Clinical Syndromes (con't.)

- Infections of prosthetic devices
- Infections related to trauma
- Bloodstream infections and sepsis syndromes
- Nosocomial infections
- Urinary tract infections
- Sexually-transmitted diseases and reproductive tract infections
- Fever (infectious and non-infectious) and hyperthermia

25

Patient Populations

- Patients who are neutropenic
- Patients with:
  - Leukemia, Lymphoma, or other malignancies
- Patients following solid organ or bone marrow transplantation/HSCT
- Patients with HIV/AIDS or patients immunocompromised by other disease or medical therapies
- Pregnant women
- Travelers and immigrants

26

Exam Content

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

For example……

27

Bacterial Diseases (27%)*

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

* percentages describe content of typical exam and are approximate

28

Bacterial Diseases (27%) - details

Approximate % of total exam

- Gram-positive rods <2%

  Which may include:

  Listeria
  Corynebacterium
  Bacillus
  Erysipelothrix

29

Bacterial Diseases (27%) - details

% of total exam

- Syndromes with bacterial pathogens 3%

  Which may include:

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

30

HIV Infection (15%)

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

31

HIV Infection (15%) - details

	Approximate % of exam
• Other complications of HIV	2%
Which may include:	
Thrombocytopenic disorders	
Hypercoagulability, Castelman's disease	
HIV infection of specific organs	
Endocrine manifestations	
• Related issues	<2%
Which may include:	
Substance abuse, Organ transplantation, Primary care, Non-HIV-related complications more common in HIV	

32

Viral Diseases (7%)

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

33

General Medicine, Critical Care and Surgery (18%)

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

34

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

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

35

Fungi (5%)

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

36

Other

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

37

- **Note:**

I recommend you take a look at the website and review the lists.

……..as an example

38

Rickettsia (2.5%)

- **R. rickettsii (Rocky Mountain Spotted Fever)**
- **R. akari (rickettsial pox)**
- **R. prowazekii (epidemic typhus)**
- **R. typhi**
- **Orientia tsutsugamushi (scrub typhus)**
- **R. conorii**
- **R. parkeri**
- **R. africae**
- **Coxiella burnetii**

39

Exam

- **Takes couple of years for new question to appear on exam and count. So new developments in last 2 years less likely to be on exam and count.**
  e.g. COVID-19, new Ebola treatment, Zika virus
- **Things that were hot and now not, are unlikely to appear:**
  - **anthrax**
  - **monkeypox**
- **Effort made not to have "look up" questions:**
  - **e.g. Treatments for uncommon parasitic diseases**
    - **Malaria - yes**
    - **Filariasis – no**

40

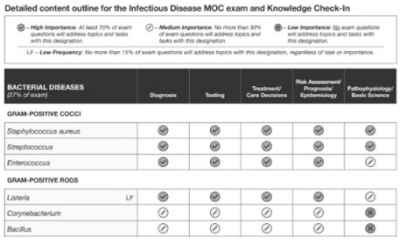
Pass rates
First-time Takers- Initial certification

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

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

41

How is MOC/KCI Content Different?


Detailed content outline for the Infectious Disease MOC exam and Knowledge Check-In

● – *High Importance*: At least 70% of exam questions will address topics and tasks with this designation.
◐ – *Medium Importance*: No more than 30% of exam questions will address topics and tasks with this designation.
○ – *Low Importance*: No exam questions will address topics and tasks with this designation.
LF – *Low Frequency*: No more than 15% of exam questions will address topics with this designation, regardless of task or importance.

BACTERIAL DISEASES (27% of exam)		Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
GRAM-POSITIVE COCCI						
Staphylococcus aureus		●	●	●	●	●
Streptococcus		●	●	●	●	●
Enterococcus		●	●	●	●	◐
GRAM-POSITIVE RODS						
Listeria	LF	●	●	●	●	◐
Corynebacterium		◐	◐	◐	◐	○
Bacillus		◐	◐	◐	◐	○

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

42

MOC Pass rate

- Maintenance of Certification (recertification):
  - Questions were from same pool as initial exam – now different blueprint

Year	#Examinees	Pass Rate (%)
2015	301	89%
2016	467	94%
2017	350	90%
2018	367	93%
2019	296	91%
2020	216	89%

43

What to do from now to exam

- Start Early!
  - Make notes of items to review just before the exam
- Know that this Board Review Course is excellent preparation
- Review questions and images from IDBR website to identify areas needing further study
- Go to ABIM website (www.abim.org) and:
  - Take the tutorial
  - Read about Exam Day: What to expect
  - See details about ID exam (blueprints, etc.)

44

What to do from now to exam

- From binders/on line presentations for this course, pull out the "handouts" covering your weak areas and make a little "binder" (e.g. parasites, fungi, mimic syndromes)
- Review your "little binder" just before exam

45

Thank You: Jack Bennett & Bennett Lorber

Good Luck
To You All !

46

Questions, Comments?

- @hboucher3
- hboucher@tuftsmedicalcenter.org
- Helen.boucher@tufts.edu

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

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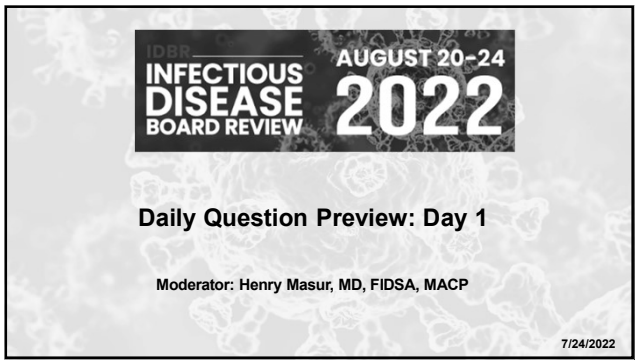
QP1

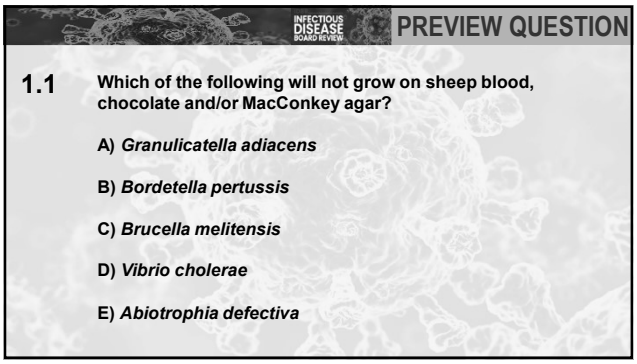
Daily Question Preview 1

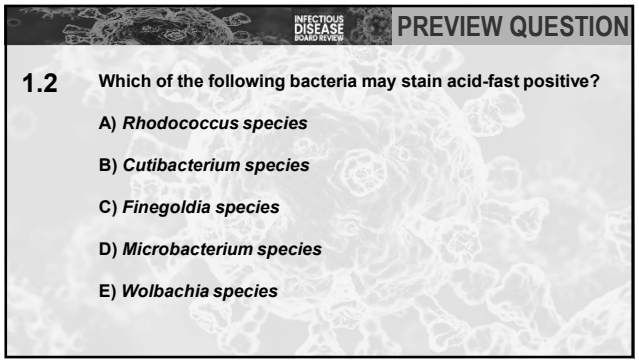
Dr. Henry Masur (Moderator)

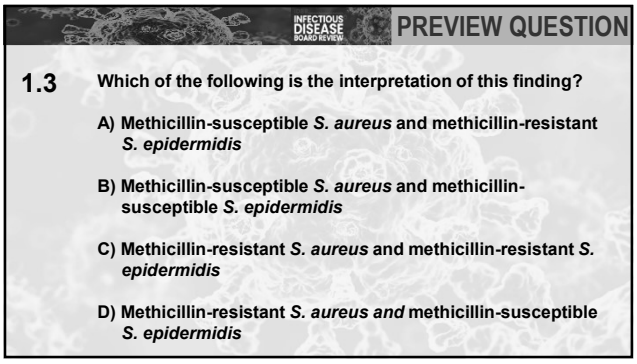
QP1 – Daily Question Preview: Day 1

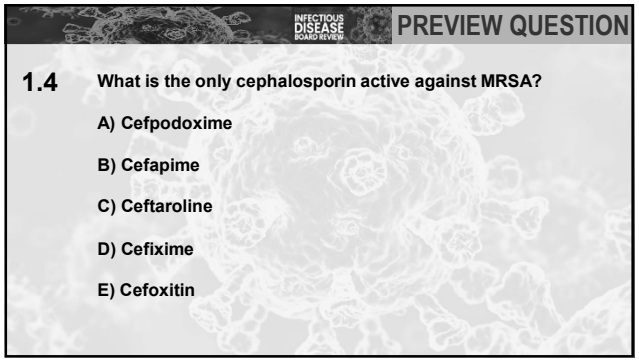
Moderator: Henry Masur, MD

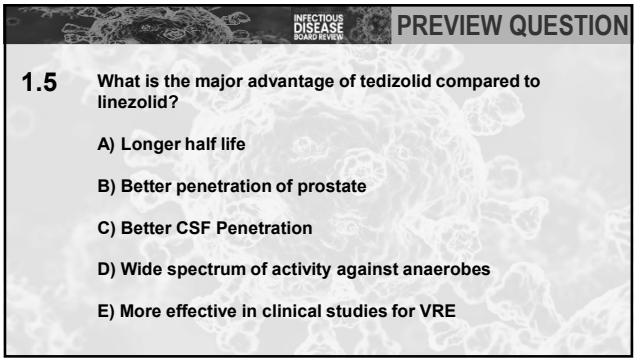












PREVIEW QUESTION

1.6 In *Staphylococcus aureus*, the protein encoded by the mecA gene is which of the following:

A) Leukocidin

B) PBP 2a

C) Oxacillinase

D) IL28 TT

E) ESBL

PREVIEW QUESTION

1.7 Which of the following would be the best choice, among the drugs listed, to treat MSSA bacteremia:

A) Doripenem

B) Imipenem

C) Ceftriaxone

D) Cefazolin

E) Aztreonam

PREVIEW QUESTION

1.8 A 63 y.o. male has COVID-19 pneumonia with a BAL-documented super-infection due to *E.coli*.

The *E.coli* is reported resistant *in vitro* to ceftriaxone, cefazolin, and aztreonam.

PREVIEW QUESTION

1.8 The *E.coli* is likely ESBL positive and is susceptible *in vitro* to the following drugs. Which drug is preferable for specific therapy?

A) Doripenem

B) Tobramycin

C) Meropenem

D) Imipenem-cilastatin-relebactam

E) Piperacillin-tazobactam

PREVIEW QUESTION

1.9 Which one of the following would you recommend as therapy for a "difficult to treat resistant" *Pseudomonas aeruginosa* outside of the urinary track?

A) Meropenem-vaborbactam

B) Ceftolozane-tazobactam

C) Cefepime

D) Ceftazidime

E) Ertapenem

PREVIEW QUESTION

1.10 Echinocandin class of antifungals has which mechanism of action:

A) inhibits synthesis of membrane sterols

B) damages cytoplasmic membrane

C) interferes with synthesis of fungal cell wall glucans

D) inhibits fungal DNA synthesis

E) interfere with synthesis of fungal cell wall chitin

PREVIEW QUESTION

1.11 45-yr-old male 6 weeks post stem cell transplant for myelodysplasia, with a history of chronic hepatitis C was discharged home to Florida on cyclosporine, mycophenolate, prednisone, Bactrim (tmp/smz), citalopram and voriconazole.

Diffuse nonpruritic erythema developed over his sun exposed skin.

PREVIEW QUESTION

1.11 The most probable cause was:

A) porphyria cutanea tarda

B) graft versus host disease

C) drug interaction

D) voriconazole

E) Bactrim allergy

PREVIEW QUESTION

1.12 A 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.

Her heterophile antibody test (Monospot) is negative. In addition to other tests, you order EBV-specific serology.

PREVIEW QUESTION

1.12 Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?

Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A)	+	+	+	+
B)	+	+	-	+
C)	-	+	+	+
D)	-	-	+	-

PREVIEW QUESTION

1.13 72-year-old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following do you recommend?

A) CT scan of chest AND Additional sputum AFB cultures

B) Empiric therapy with azithromycin, ethambutol, and rifampin

C) Additional sputum AFB cultures

D) Wait for *in vitro* susceptibility data and then treat

PREVIEW QUESTION

1.14 A 50-year-old female with alcohol substance abuse disorder suffered a provoked dog bite

- Bite was cleansed, tetanus toxoid given, and the dog placed under observation
- Patient is post-elective splenectomy for ITP; she received pneumococcal vaccine one year ago
- One day later, the patient is admitted to the ICU in septic shock with severe DIC and peripheral symmetric gangrene of the tips of her fingers/toes

QP1 – Daily Question Preview: Day 1

Moderator: Henry Masur, MD

INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

1.14 **Which one of the following is the most likely etiologic bacteria?**

A) ***Pasteurella canis***

B) ***Capnocytophaga canimorsus***

C) ***Fusobacterium sp.***

D) ***Bartonella henselae***

INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

1.15 **A 35-year-old male suffers a clenched fist injury in a barroom brawl. He presents 18 hours later with fever and a tender, red, warm fist wound.**

Gram stain of bloody exudate shows a small gram-negative rod with some coccobacillary forms. The aerobic culture is positive for viridans streptococci*

***Talan, D. CID 2003; 37: 1481**

INFECTIOUS DISEASE BOARD REVIEW

PREVIEW QUESTION

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

A) ***Viridans streptococci***

B) ***Eikenella corrodens***

C) ***Peptostreptococcus***

D) ***Fusobacterium species***

03/04

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

Microbiology Questions That Could be on the Exam

Dr. Robin Patel

03 – Core Concepts: Microbiology
04 – Microbiology: What You Need to Know for The Exam
Speaker: Robin Patel, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Core Concepts:
Microbiology: What You Need to Know for the Exam
and (some) Microbiology Questions That Could be on the Exam

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

4/20/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

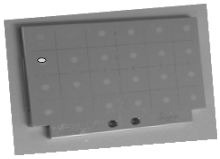
Disclosures of Financial Relationships with Relevant Commercial Interests

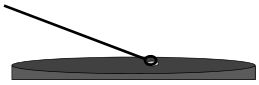
- **Contracted Research: ContraFect, TenNor Therapeutics Limited, and BioFire**
- **Consultant: Curetis, Specific Technologies, Next Gen Diagnostics, PathoQuest, Selux Diagnostics, 1928 Diagnostics, PhAST, Torus Biosystems, Day Zero Diagnostics, Mammoth Biosciences, CARB-X, Qvella, Netflix**
- **Mayo Clinic and Dr. Patel have a relationship with Adaptive Phage Therapeutics and Pathogenomix**
- **Patents: Bordetella pertussis/parapertussis PCR; device/method for sonication; anti-biofilm substance**

MALDI ToF Mass Spectrometry

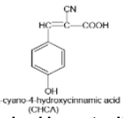
MAYO CLINIC

MALDI ToF Mass Spectrometry





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



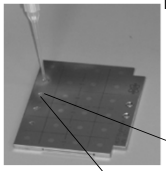
α-cyano-4-hydroxycinnamic acid (CHCA)

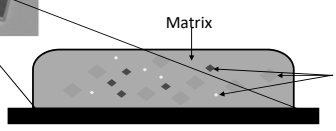
Dissolved in acetonitrile (50%) & 2.5% trifluoroacetic acid

3. **Dry – room air 5 min**

MAYO CLINIC

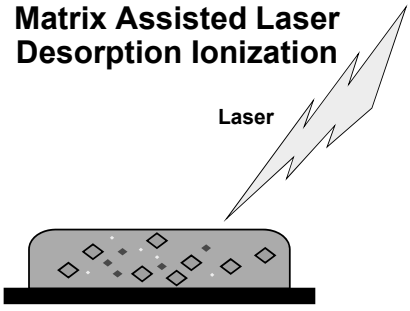
Matrix Assisted Laser Desorption Ionization





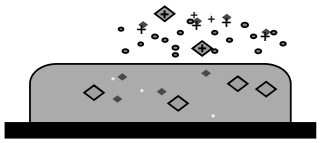
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



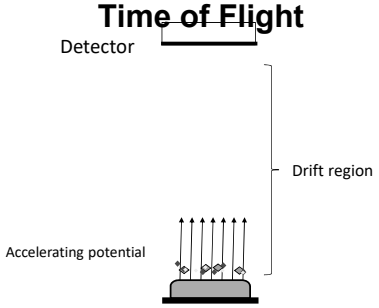
MAYO CLINIC

Matrix Assisted Laser Desorption Ionization



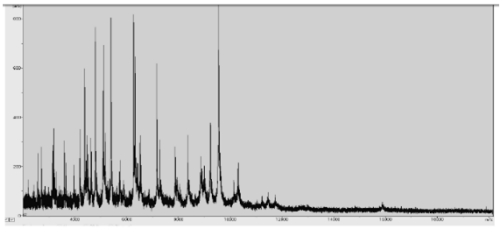
MAYO CLINIC

Time of Flight



MAYO CLINIC

Mass Spectrum Generated Compared with Library (Database)



QUESTION #1

PREVIEW QUESTION

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

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

BACTERIA REQUIRING SPECIALIZED MEDIA

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

QUESTION #2

PREVIEW QUESTION

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

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

ACID-FAST BACTERIA (MYCOLIC ACIDS)

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

QUESTION #3

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

You are asked to make a recommendation regarding postexposure prophylaxis.

QUESTION #3

Which of the following would you recommend?

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

Burkholderia pseudomallei

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

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

QUESTION #4

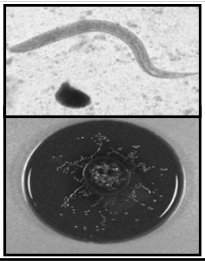
Which of the following, if present in a clinical specimen, poses a hazard for laboratory personnel?

a. Entamoeba histolytica
b. Trichuris trichiura
c. Enterobius vermicularis
d. Strongyloides stercoralis
e. Babesia microti

Strongyloides stercoralis

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

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



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

GASTROENTERITIS PANEL TESTING KEY POINTS

- If available, culture independent methods of diagnosis recommended
- Indications: Dysentery, moderate-to-severe disease, and symptoms lasting >7 days (define etiology, inform potential treatment)
- Not recommended for chronic diarrhea
- If *C. difficile* main consideration, test for *C. difficile* alone
- *Aerococcus* species not included

Riddle et al. Am J Gastroenterol 2016;111:602–622

BIOFIRE FILMARRAY MENINGITIS/ENCEPHALITIS PANEL (for reference)

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

MENINGITIS/ENCEPHALITIS PANEL KEY POINTS

- Doesn't nullify need for cell count, differential, protein, glucose, Gram stain, culture
- Cryptococcal antigen more sensitive than PCR
- *Streptococcus pneumoniae* antigen plus HSV, enterovirus and possibly VZV PCR an alternative
- May be helpful with current/recent antibiotic treatment
- HHV6 & CMV may not be clinically significant

MAYO CLINIC

Lower Respiratory Tract Panels
(for reference)

	Curetis Unyvero	BioFire
Bacteria		
Acinetobacter spp.	✓	
Acinetobacter calcoaceticus-baumannii complex		✓
Chlamydia pneumoniae	✓	✓
Citrobacter freundii	✓	
Enterobacter aerogenes		✓
Enterobacter cloacae complex	✓	✓
Escherichia coli	✓	✓
Haemophilus influenzae	✓	✓
Klebsiella oxytoca	✓	✓
Klebsiella pneumoniae	✓	
Klebsiella pneumoniae group		✓
Klebsiella variicola	✓	
Legionella pneumophila	✓	✓
Moraxella catarrhalis	✓	✓
Morganella morganii	✓	
Mycoplasma pneumoniae	✓	✓
Proteus spp.	✓	✓
Pseudomonas aeruginosa	✓	✓
Serratia marcescens	✓	✓
Staphylococcus aureus	✓	✓
Stenotrophomonas maltophilia	✓	
Streptococcus agalactiae		✓
Streptococcus pneumoniae	✓	✓
Streptococcus pyogenes		✓

	Curetis Unyvero	BioFire
Viruses		
Influenza A		✓
Influenza B		✓
Respiratory Syncytial Virus		✓
Human Rhinovirus/Enterovirus		✓
Human Metapneumovirus		✓
Parainfluenza virus		✓
Adenovirus		✓
Coronavirus (non-SARS-CoV)		✓
Fungi		
Pneumocystis jirovecii		
Resistance genes		
bla_{KPC}	✓	✓
bla_{NDM}	✓	✓
bla_{IMP}		✓
bla_{OXA-23}	✓	
bla_{OXA-24}	✓	
bla_{OXA-48}	✓	
bla_{OXA-58}		
$bla_{OXA-48-like}$		✓
bla_{VIM}	✓	✓
bla_{CTX-M}	✓	✓
bla_{TEM}	✓	
mecA	✓	
mecA/C and *MREJ*		✓

QUESTION #5

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 PREVIEW QUESTION

- You are asked to see a 62 year old man with a positive blood culture to advise on management.
- Gram stain of the positive blood culture bottle shows Gram positive cocci in clusters.
- A rapid PCR panel performed on the positive blood culture bottle contents detects *Staphylococcus aureus*, *Staphylococcus epidermidis* as well as *mecA/C* but not *mecA/C* and MREJ.

QUESTION #5

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 PREVIEW QUESTION

Which of the following is the interpretation of this finding?

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

MAYO CLINIC

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

	FilmArray BCID2	VERIGENE®	GenMark$_{Dx}$	
		Gram-Positive Blood Culture Test	ePlex BCID-GP Panel	ePlex BCID-GN Panel
Staphylococcus species	✓	✓	✓	
Staphylococcus aureus	✓	✓	✓	
Staphylococcus epidermidis	✓	✓	✓	
Staphylococcus lugdunensis	✓	✓	✓	
Streptococcus species	✓	✓	✓	
Streptococcus agalactiae	✓	✓	✓	
Streptococcus pyogenes	✓	✓	✓	
Streptococcus pneumoniae	✓	✓	✓	
Streptococcus anginosus group		✓	✓	
Enterococcus species			✓	
Enterococcus faecalis	✓	✓	✓	
Enterococcus faecium	✓	✓	✓	
Listeria species		✓	✓	
Listeria monocytogenes	✓		✓	
Bacillus cereus group			✓	
Bacillus subtilis group			✓	
Corynebacterium species			✓	
Cutibacterium acnes			✓	
Lactobacillus species			✓	
Micrococcus species		✓	✓	
Pan Gram-Positive				✓

MAYO CLINIC

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

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

*Detected as *Enterobacter* species

MAYO CLINIC

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

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

MAYO CLINIC

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

	FilmArray BCID2	GenMark$_{Dx}$		
		ePlex BCID-GP Panel	ePlex BCID-FP Panel	ePlex BCID-GN Panel
Candida albicans	✓		✓	
Candida auris	✓		✓	
Candida dubliniensis			✓	
Candida famata			✓	
Nakaseomyces glabrata	✓		✓	
Candida guilliermondii			✓	
Candida kefyr			✓	
Pichia kudriavzevii	✓		✓	
Candida lusitaniae			✓	
Candida parapsilosis	✓		✓	
Candida tropicalis	✓		✓	
Cryptococcus gattii			✓	
Cryptococcus neoformans			✓	
C. neoformans/gattii	✓			
Fusarium species			✓	
Rhodotorula species			✓	
Pan *Candida*		✓		✓

STAPHYLOCOCCI
METHICILLIN RESISTANCE

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

MAYO CLINIC

T2Direct Diagnostics
Direct from Blood

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

QUESTION #6

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

QUESTION #6

How often should this test be performed?

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

OPTIMAL FREQUENCY CMV VIRAL LOAD TESTING

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

QUESTION #7

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

QUESTION #7

Which of the following would you recommend?

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

CHROMOSOMALLY INTEGRATED HUMAN HERPESVIRUS-6

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

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

QUESTION #8

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

Which of the following is most appropriate?

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

QUESTION #9

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

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

QUESTION #9

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

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

TYPICAL SUSCEPTIBILITY OF A *bla*$_{KPC}$-PRODUCER

Klebsiella pneumoniae

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

TYPICAL SUSCEPTIBILITY OF AN ESBL-PRODUCER

Escherichia coli

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

Piperacillin-tazobactam is not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E
*Not currently recommended for infection outside of urinary tract

TYPICAL SUSCEPTIBILITY OF INDUCIBLE, CHROMOSOMALLY-ENCODED AmpC β-LACTAMASE PRODUCER

Enterobacter species*

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

Piperacillin-tazobactam is not recommended for the treatment of infections outside of the urinary tract caused by ESBL-E
*Cefoxitin S; avoid expanded-spectrum cephalosporins even if test susceptible; cefepime an acceptable choice

QUESTION #10

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

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

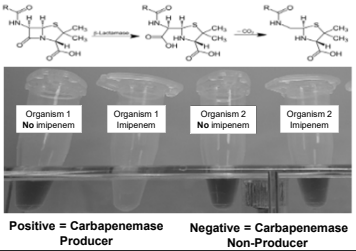
QUESTION #11

Which of the following tests for carbapenemase production?

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

CARBAPENEMASE PRODUCTION TEST

Carba NP TEST

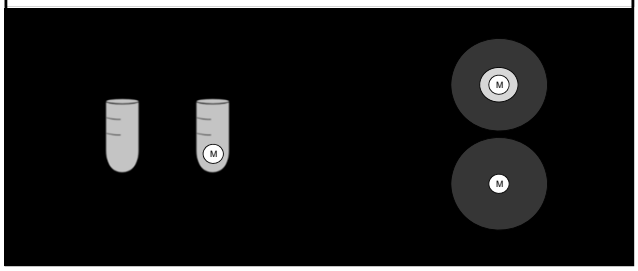


Positive = Carbapenemase Producer

Negative = Carbapenemase Non-Producer

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

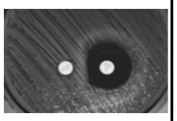
CARBAPENEMASE PRODUCTION TEST MODIFIED CARBAPENEM INACTIVATION



QUESTION #12

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

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



A. Erythromycin susceptibility, inducible clindamycin resistance

B. Erythromycin resistance, constitutive clindamycin resistance

C. Erythromycin resistance, inducible clindamycin resistance

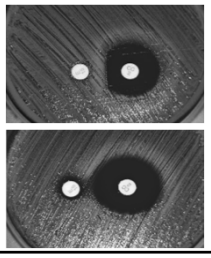
D. Erythromycin susceptibility, constitutive clindamycin resistance

INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

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

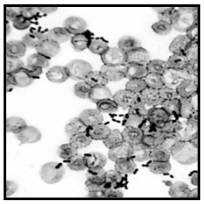
INDUCIBLE CLINDAMYCIN RESISTANCE (D-TEST)

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



QUESTION #13

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



QUESTION #13

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

A. Enterococcus gallinarum

B. Enterococcus faecium

C. Enterococcus faecalis

D. Enterococcus casseliflavus

E. Enterococcus avium

ENTEROCOCCI
VANCOMYCIN SUSCEPTIBILITY TESTING

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

QUESTION #14

A 44 year old man who underwent bilateral lung transplantation for pulmonary hypertension develops a sternal wound infection with sternal dehiscence 15 days post-transplant.
Blood cultures are negative. He undergoes sternal debridement with the finding of purulence and negative Gram and KOH stains.
After three days of incubation, pinpoint, clear colonies are visualized on cultures on sheep blood agar, however Gram stain of these colonies is negative.

QUESTION #14

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

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

Mycoplasma hominis

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

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

QUESTION #15

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

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

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

QUESTION #15

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

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

QUESTION #16

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

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

CYTOMEGALOVIRUS ANTIVIRAL RESISTANCE

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

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

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

COVID-19 DIAGNOSTICS

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

•IDSA Guidelines on the Diagnosis of COVID-19

05

Core Concepts: Antibacterial Drugs I: Gram Positive Organisms

Dr. Helen Boucher

05 – Core Concepts: Antibacterial Drugs I Gram Positive Organisms

Speaker: Helen Boucher, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

Core Concepts:
Antibacterial Drugs I Gram Positive Organisms

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

7/14/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Overview of Antibacterial Mechanisms

To Orient You: Little is Testable

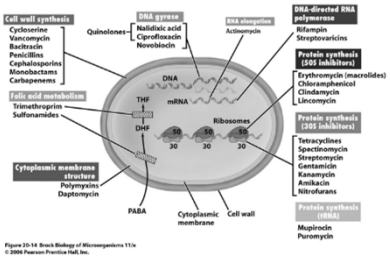


Figure 20-14 Brock Biology of Microorganisms 11/e
© 2006 Pearson Prentice Hall, Inc.

3

Cell Wall Active Agents

- Penicillins
- Cephalosporins
- Carbapenems
- Vancomycin
- Daptomycin
- Polymyxins

4

β-lactam Spectrum

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

Gram-positive

Gram-negative

5

β-lactam Antibiotics Share Mechanism of Action

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

6

β-lactam Adverse Effects

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

7

Question

PREVIEW QUESTION

- What is the only cephalosporin active against MRSA

- A) Cefpodoxime
- B) Cefapime
- C) Ceftaroline
- D) Cefixime
- E) Cefoxitin

8

Cephalosporins

- **Bactericidal**
  - **inhibit bacterial cell wall synthesis**
- **Time dependent killing**
- **Resistance due to susceptibility to β-lactamases**
- **Fewer allergic reactions than PCN**
- **CSF penetration with third generation**
- **Most renally excreted**

9

Key Points About Cephalosporin Activity

- **Enterococci**
  - **None are active**
- **MRSA**
  - **Only ceftaroline active**
- **Anaerobic activity**
  - **Only Cephamycins active**
    - **(e.g., cefoxitin, cefotetan)**
    - **Now high levels of resistance**

10

Ceftaroline Fosamil – a Prodrug (IV and IM, Not PO)

- **Activity**
  - **Gram-positive including MRSA and MDR *S. pneumoniae***
    - **Some activity vs *E. faecalis*; not *E. faecium***
  - **Limited activity vs. anaerobes**
    - **Active vs *Cutibacterium (formerly Propionobacterim) acnes, Actinomyces* spp.**

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

11

Ceftaroline Fosamil – a Prodrug (IV and IM, Not PO)

- **Activity**
  - **Active vs Gram-negative pathogens**
    - ***E. coli*, *Klebsiella* spp., *H. influenzae* (incl B-lactamase positive), *M. catarrhalis***
  - **Not *Pseudomonas* or ESBL+ GNB**
  - **Spectrum similar to ceftriaxone**
- **Bactericidal, time dependent killing**

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

12

Vancomycin

- Bactericidal (slowly)
  - inhibits bacterial cell wall synthesis
- Active against:
  - Gram Positive Aerobes
    - Streptococcus
    - Staphyloccus
    - Enterococcus
  - Gram Positive Anaerobes
    - Clostridia
    - Propionibacteria
    - Peptostreptococci
    - Actinomyces

13

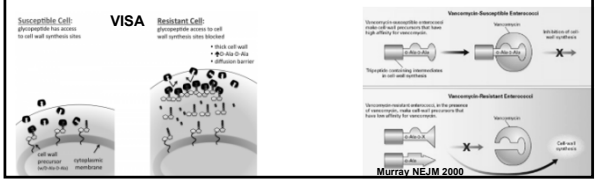
Vancomycin Resistance

- 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

14

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



Vancomycin for MRSA Bloodstream Infection

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

Dosing Calculator helps!

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

Vancomycin ADRs / Interactions

Adverse Drug Reactions

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

Drug Interactions

- Increased nephrotoxicity when given with other nephrotoxins
  - Aminoglycosides
  - NSAIDs
  - Contrast
  - Cyclosporine
  - Tacrolimus
  - Loop Diuretics
  - ACE inhibitors
  - Pip/tazo (pseudo interaction)

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Daptomycin (IV)

- Antimicrobial Class: Lipopeptide
- Broad spectrum gram + activity
  - Including MRSA
- Rapidly bactericidal
- Concentration-dependent killing
- Indications
  - cSSSI
  - *S. aureus* bloodstream infection
  - Right-sided endocarditis

Fenton C et al. *Drugs* 2004; 64: 445-55, Tedesco KL, Rybak MJ. *Pharmacother* 2004; 24:41-57, Mangili A et al. *Clin Infect Dis* 2005; 40:1058-60, Fowler VG et al. *New Engl J Med* 2006; 355:653-665

18

Daptomycin for *S. aureus* Bacteremia and Right IE

- Pneumonia
  - Do not use: surfactant binding inactivates drug
- Monitoring
  - CPK twice weekly
  - Discontinue if myopathy or CPK> 5x ULN
- Toxicity
  - Eosinophilic Pneumonia
    - Rx supportive care and steroids
  - Falsely prolonged Prothrombin Time
  - Muscle inflammation
    - CPK increase, myopathy, myositis
    - Risk factors: renal failure, statins, obesity

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Vancomycin and Daptomycin

Drug	MOA	MOR	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

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Oritavancin and Dalbavancin
Long Acting Glycopeptides

- Mechanism of Action
  - Similar to vancomycin
  - Inhibition of cell wall synthesis
- Dosing
  - Oritavancin: IV only: 1 dose (1200 mg over 3hours)
  - Dalbavancin: IV only: 1000mg, then 500mg every 7 days …OR 1500mg x 1
- Approved
  - Skin and Soft Tissue
  - Oritavancin FDA warning against use in osteomyelitis
  - Dalbavancin also used for osteomyelitis, right sided endocarditis
- Toxicity
  - Oritavancin prolongs aPTT (artificially), PT, and activated whole blood clotting time (ACT) for 5 days

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Lipo/glycopeptide Testable Toxicities

- **Vancomycin: Nephrotox.; Histamine Release**
- **Daptomycin: CPK elevation, myopathy, rhabdomyolysis; Eosinophilic pneumonia**
- **Telavancin: Nephrotoxicity**
- **Oritavancin: LFT elevation; False prolongation of aPTT**
- **Dalbavancin: LFT elevation**

22

Question

- Which quinolone has activity against MRSA

- A) Ciprofloxacin
- B) Moxifloxacin
- C) Trovafloxacin
- D) Delafloxacin
- E) Levofloxacin

23

Antibiotics Active Intracellularly

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

24

Fluoroquinolone Mechanism of Action And Resistance

- Topoisomerase inhibitors
  - Inhibits DNA gyrase and topoisomerases II and IV
  - Gyrase more for gram negs, topos for gram pos
- Resistance
  - Target site mutations
  - Drug permeability mutations
  - Occurs spontaneously on therapy
  - Susceptible to drug modifying enzymes

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Fluoroquinolones Spectrum of Gram Positive Activity

	Gram-positive	Gram-negative	Anaerobes
Cipro	Poor strep Some MSSA	Best FQ for •Pseudomonas •E coli	Some
Levo	Good strep Some MSSA	Best for *Stenotrophomonas* spp.	Some
Moxi	Good strep Good MSSA	Not effective Don't use for UTI	Best

Dr. Gilbert will address Gram-negative activity

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Fluoroquinolone Pharmacokinetics

- High oral bioavailability
  - >95% for moxi / levo, 70-80% for cipro
- Widely distributed to tissues
  - Lower than serum but therapeutic concentration in CSF, saliva, bone, ascitic fluid and prostate gland
- Elimination
  - Levo / cipro: renal through tubular secretion
  - Moxi: >60% hepatic/ biliary unchanged

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Fluoroquinolone Adverse Effects

- *C. difficile*
- Arthropathy/cartilage toxicity / tendonitis
  - FDA Warning for rare tendon rupture
    - Increased risk: advanced age, poor renal function, concomitant steroids
- Altered mental status (HA, dizziness, insomnia)
- Dysglycemia-FDA warning especially for older adults and diabetics
  - Hypo- and hyperglycemia
- Aortic aneurysm and aortic dissection-FDA warning
  - Association is controversial
- QTc Prolongation:
  Moxi > levo ? Cipro
  - Increased risk:
    - Concomitant QTc prolongers, cardiomyopathy, bradycardia, low K+ and Mg++

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Delafloxacin

- Broad spectrum fluoroquinolone
- Potential advantages:
  - MRSA activity
  - Broad spectrum including Pseudomonas
- Dosing IV and oral twice daily
- Approved for skin and soft tissue infections

Saravolatz LD and Stein GE. Clin Infect Dis. 2019;68(6):1058–62

29

Tetracyclines: Major Clinical Uses

- Acne (minocycline)
- Respiratory tract infections
  - Atypical pneumonia
- Sexually Transmitted Diseases
  - Syphilis (*T. pallidum*) – alternative therapy
  - *Chlamydia* spp.
- Tick-Borne Illnesses
  - Lyme disease
  - Anaplasmosis
  - Ehrlichiosis
  - Rocky Mountain Spotted Fever
- Community Acquired MRSA infections

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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

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New Tetracyclines

	Omadacycline	Eravacycline
FDA approval	ABSSSI, CABP	cIAI, not cUTI (failed studies)
Dosing	200 mg loading dose over 60 min day 1, 100mg IV over 30 min or 300mg orally once daily	1mg/kg IV q 12h (over 60 minutes)
	No dose adjustment for renal/hepatic impairment	Dose adjustment with hepatic impairment
Activity	Broad spectrum: Gram-pos including MRSA, VRE; Gram-neg including ESBL, CRE (not all); anaerobes	
Issues	Limited activity vs carbapenem-resistant *K. pneumoniae*	High MIC *Pseudomonas*, *Burkholderia* spp.
Safety	GI, rash, ?heart rate	GI, rash

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Question

IDBR 2022 PREVIEW QUESTION

- What is the major advantage of tedizolid compared to linezolid
- A) Longer half life
- B) Better penetration of prostate
- C) Better CSF Penetration
- D) Wide spectrum of activity against anaerobes
- E) More effective in clinical studies for VRE

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Linezolid and Tedizolid Oxazolidinone Drug Class

- Mechanism
  - binds 50s ribosome/prevents formation of initiation complex
- Spectrum of activity
  - Gram positive cocci including MRSA and VRE
    - Linezolid resistant *S.aureus* reported
  - Mycobacteria
- Resistance is rare; target change
- Linezolid bid; Tedizolid qd
- FDA approvals for Linezolid:
  - Skin and Soft Tissue, Pneumonia, VRE
  - NOT Bloodstream infection (Black Box Warning)

Shinabarger DL et al. *Antimicrob Agents Chemother* 1997; 41: 2132-36; Swaney Sm et al. *Antimicrob Agents Chemother* 1998; 42: 3251-55; French G. *Int J Clin Pract* 2001; 55: 59-63

34

Linezolid Adverse Events

- Adverse events related to mitochondrial toxicity:
  - Cytopenias
    - Monitor CBC
  - Peripheral and optic neuropathy
  - Rare:
    - Lactic acidosis, serotonin syndrome (w SSRIs)
- ↑ mortality in study of intravenous catheter-associated bacteremia

Tsiodras S et al. *Lancet* 2001;358: 207-208; Pillai SK et al. *Clin Infect Dis* 2002; 186: 1603-7; Wilson P et al. *J Antimicrob Chemother* 2003;51:186-88; Medwatch March 16, 2007

35

TMP/SMX Spectrum of Activity - Typical Bugs

- Gram Positive
  - Staphylococci: great
  - Streptococci: controversial
  - Enterococcus: not effective
- Gram Negative
  - *E. coli*: ok, increasing resistance
  - Enterobacterales: relatively effective
  - Pseudomonas / Acinetobacter: not effective
  - Stenotrophomonas: often drug of choice

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TMP/SMX Spectrum of Activity - Odd Bugs

- ***Stenotrophomonas maltophila***
- ***Listeria monocytogenes***
- ***Nocardia***
- ***Moraxella catarhallis***
- ***Pneumocystis jirovecii***
- ***Toxoplasmosis gondii*** **(but not superior to pyr/sulf)**
- ***Chlamydia*** **(but enough resistance that its not used for STDs)**
- **Atypical *mycobacteria***

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Lefamulin

- **Pleuromutilin antibiotic with IV and PO formulation**
  - **Protein synthesis inhibitor**
  - **Bacteriostatic**
- **FDA Approved community acquired bacterial pneumonia**
  - **Non-inferior to moxifloxacin for CABP in two studies**
    - **5 days of po lefamulin vs. 7 days of po moxifloxacin**

File CID 2019

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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%**

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Macrolide Spectrum

STDs

- ***Haemophilus ducreyi (chancroid)***
- ***Chlamydia spp.***

GI pathogens

- ***Campylobacter spp.***
- ***Helicobacter pylori***
- ***Salmonella typhi***
- ***Shigella spp.***

Miscellaneous Bugs

- ***Arcanobacter spp.***
- ***Bartonella henselae (cat-scratch)***
- ***Bordetella pertussis***
- ***Atypical mycobacteria***
- ***Borrelia burgdorferi***
- ***Babesia microti***

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Macrolide Adverse Drug Reactions

- **QTc Prolongation**
  - **Ery ≥ clarith > azith**
- **GI intolerance: nausea, bloating, diarrhea**
  - **Ery >> clarith >> azith**
  - **Dose related**
  - **Activity at motilin (peristalsis) receptors**
  - **Rare cholestatic hepatitis**
- **Pregnancy risk**

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Clindamycin Adverse Events

- **Allergic reactions:**
  - **Rash, fever, erythema multiforme, anaphylaxis**
- **Elevated AST/ALT**
  - **Rare progression to severe liver injury**
- **Diarrhea**
  - **Can cause severe *C. difficile* toxin-mediated colitis**
- **Reversible neutropenia, thrombocytopenia, and eosinophilia**
- **Taste disturbance**

Sanford Guide, Brit J Clin Pharmacol 64:542, 2007; Clin Med Insights Case Rep 2019 Dec 25;12:1-4

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Thank You!

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- **Kenneth Lawrence**
- **Evan Loh**
- **Paul McGovern**
- **Federico Perez**
- **Debra Poutsiaka**
- **George H. Talbot**
- **Our patients and their families**

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Questions, Comments?

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Appendix

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Penicillins

Rx	Spectrum	Additional Adverse Events
Penicillin (oral/IV)	Group A strep; Syphilis	
Oxacillin/nafcillin (IV)	MSSA	AIN
Amoxicillin (oral) **Ampicillin** (IV)	Amox and amp have similar spectrum and are both broader than penicillin More active against H. flu, E. coli, Enterococcus, Listeria	
Amoxicillin clavulanate (oral) **Ampicillin sulbactam** (IV)	Broader spectrum than amox/amp due to addn of a beta-lactamase inhibitor; improved bioavilability (BID) Some activity against S. aureus; more active against H. flu and other gram negatives due to stability to some beta-lactamases NOT active against Pseudomonas Active against oral and gut anaerobes	Delayed hepatotoxicity (amox/clav)
Piperacillin tazobactam (IV)	Broader than amp/sulbactam Active against gram positive organisms including streptococci Broad activity against gram negatives incl Pseudomonas	

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Cephalosporins

Rx	Spectrum	Additional Adverse Events
1st Gen Ceph **•Cefazolin** **•Cephalexin**	Staph and strep MSSA Some gram negatives including E. coli, Klebsiella, Proteus although 1st generation cephalosporins are very susceptible to beta-lactamases	
2nd Gen Ceph **•Cephamycin** **•Cefuroxime**	Gram positive cocci H. flu, E. coli, Klebsiella Cephamycin – active vs anaerobes, in vitro vs ESBLs (no clinical data)	
3rd Gen Ceph **•Ceftriaxone**	Streptococci pneumoniae (excellent) Gram negative rods but NOT Pseudomonas Excellent CSF penetration Drug of choice for bacterial meningitis	Biliary sludge
4th Gen Ceph **•Cefepime**	Broad gram positive and broad gram negative activity, including Pseudomonas Often used as empiric therapy in hospitalized patients (however may need to add vancomycin to treat MRSA)	Potential neurotoxicity, especially in patients with renal failure
5th Gen Ceph **•Ceftaroline**	Broader than amp/sulbactam; ceftriaxone-like Prodrug Active against gram positive organisms including streptococci and broad activity against gram negatives not incl Pseudomonas	

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Ceftaroline Clinical Use

- **Acute bacterial skin and soft tissue infections**
- **Community Acquired Pneumonia**
- ***S. aureus* bloodstream infection**
  - **Controversial-see Chambers Lecture**
- **Controversy over dosing regimen**
  - **600mg twice daily – FDA-approved regimen**

Lodise & Low, Drugs, 2012; Saravolatz et al. CID 2011: 52: 1156; File et al. CID 2010; 51: 1395; Zasowski et al, AAC 2017;61(2),e02015-16; Geriak et al. AAC 2019; 63(5); Kalil et al. AAC 2019; 63(11)

48

Ceftaroline Safety and Monitoring

- Hypersensitivity 1-3%, rash 3%
- GI - nausea, vomiting, diarrhea 5%
- Hematologic toxicity (class effect)
  - Eosinophilia
  - Positive Coomb's test, rarely clinically significant
- Hepatotoxicity – LFT abn 1-7%
- Nephrotoxicity rare
- Neurotoxicity – tremor, confusion, seizure, encephalopathy
  - Worse with renal failure

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Oritavancin - Lipoglycopeptide With Long Half-life

- Mechanism of action
  - inhibition of cell wall synthesis and disrupts bacterial membrane
  - Gram-positive spectrum
    - *S. aureus*, MRSA, VISA, VRSA, GAS, *S. anginosus* group
    - *E. faecalis* , *E. faecium*/VRE (active vs VanA, VanB, Van C, Van D)
- Bactericidal
- IV only, 1 dose
  - 1200 mg over 3 hours
- Cytochrome P450 enzyme – warfarin interaction

- FDA approved
  - ABSSSI

HF Chambers NEJM 2014; 370(23): 2238. WWW.FDA.GOV.
Arias et al CID 2012: 54 (Suppl 3): S233; GR Corey et al. NEJM 2014; 370(23): 2180-2190

50

Dalbavancin - Lipoglycopeptide With Long Half-life

- Gram-positive spectrum
  - *S. aureus*, MRSA, VISA, GAS
  - Low MRSA MICs
  - Enterococci – inactive vs VanA
- Mechanism of action – cell wall synthesis inhibit
- Bactericidal
- IV only (dose over 30 min), long half-life (app 8.5 days)
- Dosing
  - 1000mg, then 500mg every 7 days OR 1500mg x 1
  - Decrease dose by 25% for CrCl <30ml/min, not dialysis
- FDA approved ABSSSI

Dowell et al. *Critical Care* 2008, 12(Suppl 2):P26. www.fda.gov
Nailor and Sobel. Infect Dis Clin N Am 23(2009): 965. Jauregui et al. CID 2005; 41: 1407; Dunne et al CID 2016
HW Boucher, M Wilcox, GH Talbot, S Puttagunta, AF Das, MW Dunne. NEJM 2014; 370(23): 2169

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Dalbavancin

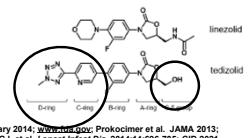
- Other uses
  - Limited data, varying dosing regimens
    - Endocarditis and osteomyelitis
    - Persons who inject drugs
- Case reports of failure with emergence of VISA, presumably associated with low-level drug exposure
  - One patient had VISA detected in urine while on dalbavancin for CLASBI
  - One patient was pregnant and had failure of therapy for IE

- Steele JM et al. J Clin Pharm Ther. 2018;43:101-103.
- Werth BJ et al. Clin Microbiol Infect. 2018;24:429.e1-429.e5.

52

Tedizolid - Oxazolidinone Drug Class Once Daily Dosing, Lower Dose

- Non-antibiotic antibacterial; a MAO inhibitor
  - Inhibits protein synthesis, bactreiostatic
    - Binds peptidyl transferase region of bacterial ribosome prevents binding of amino acyl tRNA
- Gram-positive spectrum
  - *S. aureus*, MRSA, VISA, GAS, *S. agalactiae*, *S anginosus* group, *E. faecalis* (vanco-susceptible only)
- IV and oral
- Half-life 12 hours, once daily dosing
- 200 mg daily x 6 days
  - No dose adjustment for age, renal/hepatic impairment
- FDA approved ABSSSI
- HABP/VABP Study Failed



Moellering CID January 2014; www.fda.gov; Prokocimer et al. JAMA 2013;
Moran GJ, et al. *Lancet Infect Dis.* 2014;14:696-705; CID 2021

53

Sulfonamides & TMP/SMX

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

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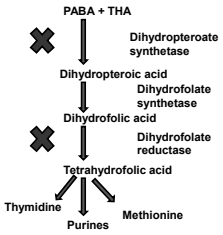
TMP/SMX Mechanism of Action

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



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TMP/SMX Resistance Mechanisms

Sulfamethoxazole

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

Trimethoprim

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

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TMP-SMX Adverse Effects

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

- Gastrointestinal effects
- "Nephrotoxicity"
- Fever
- Drug-drug interactions
- Hyperkalemia

HIGH PLASMA PROTEIN BINDING

COMPETES FOR TUBULAR SECRETION

57

Clindamycin

- Mechanism of action
  - Protein Synthesis Inhibitor
  - Binds 50s Ribosome

Clin Infect Dis. 2014; 59:698-705J Antimicrob Chemother. 2019 Jan 1;74(1):1-5

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Protein Synthesis Inhibitors - Summary

Drug	Mech of Action	Mech of Resist	Spectrum	Clinical Uses	Major Adverse Effect
Linezolid	50s	Mutation in ribosome	Gram + (resistant)	MRSA, VRE	Pancytopenia Serotonin syndrome
Tetracyclines (Doxycyline)	30s	Target site modification Efflux	Comm acq MRSA, atypical pneumonia pathogens, Lyme, rickettsia and other tick borne pathogens, Treponema pallidum	Lyme, RMSF, Comm Acq MRSA, acne, CABP	Enamel hypoplasia, photosensitivity Esophageal ulceration
Aminoglyco-sides	30s	Inactivating enzymes Efflux Ribosomal mutations	GNRs	serious gram negative infx	Nephrotoxicity Oto-vestib toxicity
Macrolides	50s	Target site modification Efflux	Gram + Atypical PNA pathogens	Atypical pneumonia, resp infx	p450 drug interactions GI upset QT prolongation
Clindamycin	50s	Target site modification Efflux Inactivate drug	Gram +, Anaerobes	Oral and intra-abd infx	*C. difficile* colitis

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06

Antibacterial Drugs I: Key Points and Questions that Could be on the Exam

Dr. Helen Boucher

06 – Antibacterial Drugs I: Key Points and Questions That Could be on the Exam

Speaker: Helen Boucher, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antibacterial Drugs:
Key Points and Questions That Could Be On the Exam

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7/17/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Question 1

IDBR 2022 PREVIEW QUESTION

In *Staphylococcus aureus*, the protein encoded by the mecA gene is which of the following:

A Leukocidin
B PBP 2a
C Oxacillinase
D IL28 TT
E ESBL

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Question 2

IDBR 2022 PREVIEW QUESTION

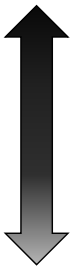
Which of the following would be the best choice, among the drugs listed, to treat MSSA bacteremia

A) Doripenem
B) Imipenem
C) Ceftriaxone
D) Cefazolin
E) Aztreonam

4

β-lactam Spectrum

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



Gram-positive

Gram-negative

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Question 3

Which of the following has microbiologic and clinical activity against *Enterococcus faecalis*

A) Cefazolin
B) Ceftriaxone
C) Imipenem
D) Aztreonam
E) Piperacillin-tazobactam

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Important Resistant Gram+ Organisms

- Enterococcus
  - Resistant: All cephalosporins and monobactams
- MSSA
  - Resistant: All penicillin and monobactams
  - Ceftriaxone does NOT work well
- MRSA
  - Resistant: All beta-lactams except ceftaroline

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IV and Oral MRSA Drugs

IV
- Vancomycin
- Daptomycin
- Linezolid/Tedizolid
- Ceftaroline
- Telavancin
- Minocycline
- Clindamycin
- Dalbavancin/Oritavancin
- Delafloxacin

Oral
- Linezolid/Tedizolid
- TMP-SMX
- Doxy/minocycline
- Clindamycin
- Delafloxacin

Combination Therapy
- See Chambers lecture

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Drug Regimens Active Against VRE (*E. faecium*) Resistant to Vancomycin and Ampicillin

- Linezolid (FDA approved)
- Daptomycin plus probably one of following
  - Ampicillin or ceftaroline or ceftriaxone
- Ampicillin if amp MIC <=32 mcg/ml
- Ampicillin-sulbactam
  - if resistance due to beta lactamase production
- Not Quinupristin/dalfopristin-FDA approval withdrawn for VRE
- For cystitis (not pyelonephritis)
  - Nitrofurantoin
  - Fosfamycin

**E faecalis* resistant to vanco are often susceptible to ampicillin

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Question 4

What is the mechanism of action for vancomycin resistance for *Staphylococcus aureus*

A) Mec A
B) Efflux pump
C) Change in vancomycin binding site on peptidoglycan
D) Porin

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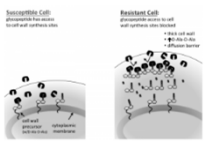
Vancomycin Resistance

- VISA
  - Thick walls, generous binding sites…
- Vancomycin resistance
  - Not in Streptococcus
  - RARE in Staphylococcus
  - Common in Enterococcus
    - Rare in *E. faecalis* (4% in 2014)
    - Common in *E. faecium* (71% in 2014)
    - Mechanism
      - Change in vancomycin binding site on peptidoglycan



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Question 5

Eosinophilic pneumonia is a complication of which of the following:

A) Ceftaroline
B) Delafloxacin
C) Doripenem
D) Daptomycin
E) Linezolid

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Question 6

Drug interference with clotting tests are most often a complication of which of the following

A) Vancomycin

B) Linezolid

C) Dalbavancin

D) Oritavancin

E) Tedizolid

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Question 7

- How common is vancomycin resistant *S. aureus* (VRSA) in the United States
- A) 20% isolates
- B) 10% isolates
- C) <5% isolates
- D) < 50 total isolates
- E) Zero

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Question 8

- Which of the following glycopeptides has the best activity against *C. difficile*
- A) Dalbavancin
- B) Oritavancin
- C) Telavancin
- D) Vancomycin
- E) Teicoplanin

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Question 9

Which of the following would be a bad choice to treat a urinary tract infection empirically

A) Ciprofloxacin

B) Levofloxacin

C) Moxifloxacin

D) Delafloxacin

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Question 10

A 55 year old man undergoes emergency surgery for a ruptured appendix with severe bacterial peritonitis and septic shock.

He has no antibiotic allergy or intolerances.

Which one of the following antibiotics requires concomitant metronidazole IV?

A **Piperacillin-tazobactam**
B **Ampicillin-sulbactam**
C **Cefepime**
D **Imipenem-cilastatin-relebactam**
E **Eravacycline**

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Question 11

Which of the following drugs can cause hyperkalemia

A) Linezolid

B) Delafloxacin

C) Trimethoprim

D) Daptomycin

E) Eravacycline

18

TMP-SMX Adverse Effects

- **Anaphylaxis**
- **Skin rashes**
- **Bone marrow toxicity**
- **Hemolysis (G6PD def)**
- **Hepatitis**
- **Gastrointestinal effects**
- **"Nephrotoxicity"**
- **Fever**
- **Drug-drug interactions**
- **Hyperkalemia**

TMP COMPETES FOR TUBULAR SECRETION

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Good Luck!!

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Questions, Comments?

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

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BR1

Board Review Session 1

Drs. Masur (Moderator), Boucher, Gandhi, Gilbert, Kotton, Patel, and Winthrop

BR1 – Board Review: Day 1

Moderator: Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Board Review: Day 1

Moderator: Henry Masur, MD
Faculty: Drs. Boucher, Gandhi, Gilbert, Kotton, Patel, and Winthrop

BOARD REVIEW DAY 1

#1 **A 39-year-old male presented with fever, chills, and fatigue for one month; he has developed a dry cough over the past two weeks. On exam he is febrile to 103F but otherwise has normal vital signs.**

He is found to have oral thrush, enlarged but mobile and soft, non-tender bilateral anterior and posterior cervical lymph nodes, and hepatosplenomegaly.

His labs show Hbg 5.0 g/dl, WBC 6.0/mm^3, Platelets 78000/mm^3.

He is found to be HIV positive (CD4=7, Viral load 1.8 million).

C reactive protein= 90mg/L (Normal: Less than 10 mg/L); Serum ferritin 2650 (ULN=450), and normal peripheral smear.

HHV-8 qPCR: 45,000,000; copy/mL.

BOARD REVIEW DAY 1

#1 **Chest CT shows mediastinal, axillary and cervical adenopathy.**

Abdominal CT shows hepatosplenomegaly and diffuse adenopathy.

His bone marrow biopsy shows a hypercellular marrow with interstitial HHV8-positive cells and polyclonal plasma cells.

An extensive workup for other bacterial, fungal and viral pathogens is not contributory

PET Scan

- Bilateral scalene lymphadenopathy
- Hepatosplenomegaly
- Diffuse hypermetabolic activity of the axial and appendicular skeletal system

BOARD REVIEW DAY 1

#1 **The therapy most likely to be effective for this complication of HIV, in addition to starting antiretroviral therapy, would be:**

A) Ganciclovir
B) Ribavirin
C) Dexamethasone
D) Alemtuzumab (Campath)
E) Rituximab (Rituxan)

BOARD REVIEW DAY 1

#2 **An 18-year-old woman in Portland, Oregon presented to an acute care office because of a 4-day history of redness and pain in her upper ear beginning two days after an ear piercing at a shopping mall.**

She had seen her pediatrician two days prior because of pain in the insertion site and was given cephalexin to take four times daily.

She took the medication as prescribed but the pain had become increasingly severe over the next two days and today, a Sunday, she had not been able to be seen again by her pediatrician.

BOARD REVIEW DAY 1

#2 **She was otherwise healthy and has no history of boils or other notable skin infections.**

On examination she was afebrile and had marked erythema, tenderness and swelling on the upper margin of her left ear around a small gold stud. No pus was seen or could be expressed by gentle pressure on the wound site.

There was no local adenopathy.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#2 **The most useful therapeutic maneuver, in addition to extracting the stud, would be to modify the cephalexin regimen with which of the following:**

A) Add ciprofloxacin
B) Add metronidazole
C) Add valacyclovir
D) Change cephalexin to amoxicillin-clavulanate
E) Add a single IV dose of ceftriaxone

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#3 **A 62-year-old male computer engineer from Seattle is 90 days post allo-HSCT for myelodysplastic syndrome and has been receiving valacyclovir prophylaxis.**

The patient has had several episodes of severe graft versus host disease, twice associated with CMV detection in the blood by PCR, for which valganciclovir was substituted for valacyclovir for 2 to 3 week periods with good clinical response, with the most recent course ending 4 weeks ago.

Two weeks ago the patient had onset of fever and severe diarrhea. Reappearance of CMV in the blood by PCR led to initiation of intravenous ganciclovir on the third day of diarrhea

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#3 **Persistence of diarrhea for seven days despite high dose steroids for presumed GVHD of the colon led to infectious disease consultation.**

Stool was negative for *Clostridium difficile* toxin by PCR and the CMV PCR in blood was unchanged after a week of ganciclovir.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#3 **What would be the most appropriate next step?**

A) Oral metronidazole
B) Oral vancomycin
C) Change from ganciclovir to foscarnet
D) Colonoscopy
E) Stool for Strongyloides

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#4 **A 24-year-old female had completed her fifth course of cytotoxic chemotherapy for squamous cell carcinoma of the oropharynx.**

She had an absolute neutrophil count of 5/cu mm and platelet count of 7,000/cu mm when she developed the sudden onset of fever to 40°C but was otherwise stable.

Two blood cultures were drawn through the tunneled subclavian catheter, and one culture was drawn peripherally.

The tunneled subclavian catheter exit site and tunneled area were non-tender and look unremarkable on physical examination. There is no exit site inflammation or exudate.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#4 **Two blood cultures drawn through the line and the peripheral blood culture are positive for E. coli which is sensitive to fluoroquinolones, cephalosporins, and aminoglycosides.**

There is no indication of a source of the bacteremia other than the line.

CT of the abdomen with contrast is unrevealing as is a urinalysis. The referring team encourages you to try to salvage the line.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#4 What management would you recommend?

A) Remove the catheter and treat with ceftriaxone

B) Remove the catheter and treat with ceftriaxone plus 3 days of gentamicin

C) Retain the catheter and treat with ceftriaxone

D) Retain the catheter and treat with ceftriaxone and 3 days of gentamicin

E) Retain the catheter and treat with ciprofloxacin and 3 days of gentamicin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#5 Multiplex PCR platforms are now available in most diagnostic laboratories to determine cause of diarrhea.

Which of the following indications is an appropriate indication for ordering a diarrhea stool study for a broad range of pathogens by one of these platforms?

A) Acute diarrhea of 7 days

B) Persistent diarrhea of 16 days

C) Gastroenteritis with vomiting

D) Patient with ulcerative colitis with flare

E) Patient suspected to have C. difficile diarrhea

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#6 Three United States Special Forces officers reported to sick call with a similar complaint of moderately severe, diffuse muscle pain, low-grade fever and malaise.

Physical examination was normal except for diffuse muscle tenderness and some puffiness around the eyes.

Routine laboratory work was normal except for total eosinophil counts of 700-1000/cu mm and a CPK twice the upper limit of normal.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#6 All three patients had been on a joint training mission in Brazil, during which they had spent nights in the jungle, waded in streams and had numerous insect bites.

At the end of the mission they had eaten at a barbecue of roast pig with other local foods.

Mefloquine was used for malaria prophylaxis. Symptoms began approximately two weeks after their return to the United States.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#6 The most likely cause of their illness would be which of the following?

A) Trypanosoma cruzi

B) Trichinella spiralis

C) Leishmania brasiliensis

D) Wuchereria bancrofti

E) Leptospira interrogans

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#7 Which one of the following is the most likely mechanism of the resistance to the polymyxins, polymyxin B and colistin (polymyxin E)?

A) Enzymatic modification of the polymyxin

B) Change in the drug site of action

C) Shedding of capsular polysaccharides

D) Presence of a plasmid-mediated efflux pump

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#8 **A 26-year-old woman has been receiving acupuncture for depression.**

Four months after beginning acupuncture, she developed three tender 1-3 cm lesions at acupuncture sites on her neck.

She is otherwise healthy and has a normal lab profile.

Biopsy shows granulomas with acid-fast organisms. Culture is pending.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#8 **The best option would be:**

A) Do nothing until culture result is available

B) Treat with INH, rifampin, PZA, and ethambutol

C) Follow for several months and treat if they do not resolve

D) Perform excisional biopsy of the three lesions

E) Treat with rifampin and ethambutol

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#9 **A 45-year-old male from Colorado whom you are following for long-term treatment of chronic osteomyelitis returns to your office complaining of decreasing vision of two weeks' duration.**

After an initial course of vancomycin, long term suppression with linezolid 600 mg po bid was begun three months ago.

Four weeks ago numbness and tingling of his fingertips led to a diagnosis of peripheral neuropathy and pregabalin (Lyrica) was started.

Two weeks prior, he noted blurring of vision in his left eye. He consulted an ophthalmologist who reported vision of 20/400 in both eyes.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#9 **The anterior chamber, vitreous and retinas were normal except for some blurring of the disc margins bilaterally and a pale sector in the right disc. Intraocular pressure was normal bilaterally.**

He diagnosed optic neuritis and prescribed prednisone 40 mg daily. After two weeks, there was no improvement.

The patient drinks 4 to 6 beers a day, and was treated for syphilis two decades previously. A VDRL was negative and the FTA was positive.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#9 **His medications are linezolid and pregabalin.**

The patient admits to a sexual encounter with a prostitute while on a business trip 6 weeks ago.

He likes to go camping and is aware of numerous mosquito bites but not ticks.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#9 **Which one of the following is the most likely diagnosis?**

A) Pregabalin toxicity

B) CNS syphilis

C) Lyme

D) Thiamine deficiency

E) Linezolid toxicity

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#10 **A 45-year-old woman undergoes a third kidney transplant.**

She is highly sensitized (has HLA antibodies that put her at higher risk of rejection) and is thus maintained on high doses of immunosuppression.

Her regimen includes belatacept, mycophenolate mofetil, and prednisone.

Her donor was CMV IgG positive, she was CMV IgG negative (D+R-) and she was maintained on valganciclovir prophylaxis.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#10 **She now has a rising CMV viral load (44,000 IU/ml on plasma) on treatment dose valganciclovir (900 mg twice a day). She feels a bit fatigued and has some diarrhea, with no visual changes or other symptoms.**

Her transplant doctors are reluctant to reduce immunosuppression further.

Genotyping of CMV in her peripheral blood showed a A594V mutation in the UL97 gene, which has been associated with high-level resistance to ganciclovir.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#10 **What would you recommend to treat her CMV disease?**

A) High dose valacyclovir 8 grams/day

B) CMV immunoglobulin

C) High dose intravenous ganciclovir

D) Maribavir

E) Letermovir

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#11 **A *Staphylococcus aureus* isolate is highly resistant to vancomycin (VRSA).**

Vancomycin resistance in this isolate is likely mediated by which of the following gene clusters?

A) *mecA*

B) *vanA*

C) *vanB*

D) *vanC*

E) *ileS-2*

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#12 **A 37-year-old male construction worker from Mexico was referred because of new skin lesions, arthralgias, and fever.**

The patient had been diagnosed with lepromatous leprosy 4 months earlier and started on dapsone, rifampin, and clofazimine.

He was found to be HIV positive, with a CD4+ count of 350/cu mm and a viral load of 50,000 copies/ml. Antiretrovirals were not begun.

A few days prior to consultation, the patient had the onset of fever, arthralgias and new skin lesions.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 **BOARD REVIEW DAY 1**

#12 **On examination his temperature was 39.5°C.**

In addition to his prior skin nodules and plaques, he had several new, tender, red, nodular lesions on his face and anterior aspect of his lower extremities.

Routine CBC and chemistries were unremarkable. A CRP was 45.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#12 **The most likely course of action to benefit this patient is which of the following:**

A) Hold dapsone and rifampin
B) Start thalidomide
C) Start ethambutol
D) Stop clofazimine
E) Biopsy a skin lesion for culture

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#13 **A 27-year-old man is brought by ambulance to the emergency room. His mother came home at the end of her workday and found him delirious on the living room couch. When she touched him, he was "burning up," and she called for emergency service.**

In the emergency room his temperature is 103.4°F, his heart rate is 132, and his blood pressure is 88/56mmHg. He is not responsive to commands and mumbles incoherently.

He has an abdominal scar that his mother reports is due to a splenectomy, the result of trauma from a motorcycle accident when he was 19 years old.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#13 **There is a deep abrasion on his right lateral calf that was erythematous, but not purulent. His mother reports that he scraped his leg 5 days ago when he slipped and fell off a stone wall while helping her plant spring flowers. He also had an encounter with a stray dog that bit him when he tried to move the dog out of his yard.**

The patient is up to date on his vaccinations.

His white blood cell count is 24,700 with 19% band forms.

The lab calls to say that they think they see small rod-shaped bacteria on the Wright-stained blood smear.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#13 **His illness is most likely due to which one of the following?**

A) Streptobacillus moniliformis
B) Haemophilus influenzae
C) Vibrio vulnificus
D) Capnocytophaga canimorsus
E) Pasteurella canis

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#14 **A 25-year-old female with acute myelogenous leukemia is currently in complete remission and is being scheduled for an allogeneic stem cell transplantation in the near future.**

The patient's CMV IgG is positive, and her identified donor's CMV IgG is negative.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 1

#14 **Which of the following would you recommend regarding prevention of CMV infection post-transplantation?**

A) Letermovir
B) Brincidofovir
C) Acyclovir
D) Monthly IVIG
E) Valganciclovir

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#15 **A 50-year-old 5'10", 278 lb (BMI 40) male is admitted for treatment of weeping bilateral lower leg "cellulitis not responding to outpatient therapy with oral amoxicillin/clavulanate."**

Leg swelling is of several months' duration but the fluid oozing is of recently origin and worse after standing all day at his job. He recently quit work for that reason.

On exam, temp 37.2C with otherwise normal vital signs.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#15 **Both lower legs and feet are red, edematous, pit slowly to pressure, and minimally tender. The skin has some loose blebs that are oozing sticky fluid. There is an underlying brownish hue to the skin.**

Pulses are detectable with Doppler.

There is evidence of both tinea pedis and onychomycosis.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 1**

#15 **Which one of the following is the most likely diagnosis:**

A) Erysipelas
B) Stasis dermatitis
C) Erythrasma
D) Staphylococcal scalded skin syndrome

07/08

Core Concepts: Antibacterial Drugs II: Gram Negative Organisms

Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam

Dr. David Gilbert

07 – Core Concepts: Antibacterial Drugs II Gram Negative Organisms
08 – Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam

Speaker: David Gilbert, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antibacterial Drugs Active vs Gram Negative Bacteria: Part 1

David N. Gilbert, MD
Infectious Diseases Emeritus,
Providence Portland Medical Center
Professor of Medicine
Oregon Health and Science University

7/17/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultant: Biomerieux
- Research Grant on Diagnostics from Biofire

Structure of Presentation of Testable Topics

- First, "Hot" General Principles
- Then, discuss antibacterials from the perspective of targeted /identified gram-negative bacteria
- My Part 1 is here; Part 2 is available anytime on line
- Dr.Boucher will focus on antibacterials active vs gram-positive bacteria

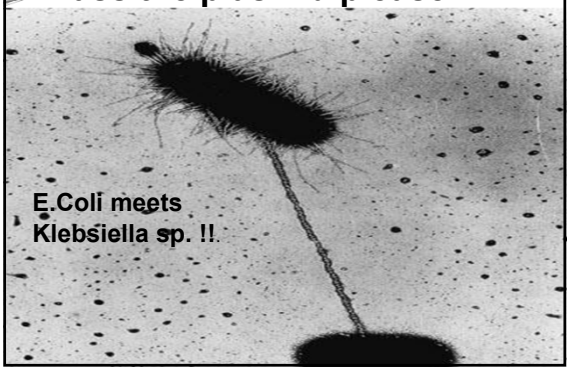
What determines antibiotic choice ?

- It's not just in vitro susceptibility and allergy history.
- Preferred choices: Effective in clinical use and Guideline recommended
- Alternative preferred choices:
  - Active in vitro, part of an active drug class, but:
    - Broad spectrum, toxicity, and/or limited clinical use
- Variable choices.
  - Active in some but not all settings
  - Maybe effective in combination
  - Low barrier to development of resistance

Reasons Drug is not Recommended

- Resistance of target organism(s) in vitro
- Poor penetration of drug to site of infection
- Severe and/or frequent toxicity
- Risk of severe hypersensitivity reaction
- Insufficient supportive clinical efficacy data

"Pass the plasmid please "



E.Coli meets Klebsiella sp. !!

Major Gene-Expressed Mechanisms of Resistance to Antibacterials

- Enzymatic inactivation
- Target site absent: intrinsic resistance
- Target site modification or protection of target site (high level of resistance)
- Excessive non-lethal binding sites
- Reduced cell wall permeability (porin closure)
- Drug efflux pumps (low level resistance)
- Multiple mechanisms may be present

Combination vs Mono-Antibacterial Therapy

- Combination therapy:
  - Decreases risk of selection of resistant subpopulations
  - Empirically in patient at risk of infection due to MDR GNB ;
    - Increases likelihood of at least one active drug
  - Required for efficacy: e.g. Enterococcal Infective Endocarditis ; M.tbc.
  - Adjunctive:
    - Addition of clindamycin for toxic shock toxin
    - Addition of rifampin for penetration of biofilms on prostheses

Three clinicald examples of need for bacteriocidal therapy

1. **Febrile Neutropenic Patients**
2. **Infective endocarditis**
3. **Bacterial meningitis**

PK/PD.

- Concentration-dependent killing and long persistent (post-antibiotic) effect ?
  - *AGs, daptomycin, and FQs*
- Killing dependent on time above MIC, no persistent [post-antibiotic] effect?
  - *Penicillins, cephalosporins, aztreonam, and carbapenems*
- Killing depends on time above MIC and a persistent Post-Antibiotic effect?
  - *Vanco., macrolides, tetra, linezolid, clinda*

Variables in Dosing

- Allergy
- PK/PD
- Body weight
- Elimination:
  - Renal
  - Liver: e.g.: Induction/inhibition cytochrome P450 enzymes
- Dose related toxicity; Use of TDM

Beta-Lactams

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams (e.g.,Aztreonam)
- Share: presence of a beta-lactam ring, potential for causing seizures, and allergenicity

Speaker: David Gilbert, MD

To survive bacteria are constantly mutating

- More than 4500 beta-lactamases reported
- Promiscuity is rampant among bacteria
- Not unusual to detect more than one mechanism of resistance: e.g.,
  - Target change &/or Target Protection
  - Active efflux pumps
  - Decrease in cell wall permeability
  - Phenotypic antibiotic suscept. Testing does not identify specific mechanism(s) of resistance
- IF patient fails clinically and/or failure to eradicate pathogen, whole genome sequencing can identify specific mechanisms
- NO surprise: it is hard to write "resistance " test questions

Ambler Molecular Classification of Beta-Lactamases*

Class	Subtypes	B-L-ase Inhibitor	Substrates
A	ESBLs + serine carbapenemases (e.g. KPCs)	Clavulanic, Avibactam, Rele & Vaborbactam	ESCs Carbapenems
B (BAD!)	Metallo-carbapenemases	EDTA(lab testing only)	All beta-lactams except aztreonam & Cefiderocol
C	AmpC	Tazo and Avibac.	Cephalosporins
D	Oxa-48 Some ESBLs Serine carbapenemases (e.g., KPCs)	Avibactam Clavulanic Avibactam & Vaborbactam	Penicillins, Carbapenems, ESCs, & Aztreonam ESCs and Carbapenems

*Ambler: Based on nucleotide sequencing

Antibacterial activity of Piperacillin-Tazobactam

- Active vs.:
  - Majority of *Enterobacterales (formerly Enterobacteriaceae*)
  - *Bacteroides fragilis*
  - Maybe *Pseudomonas aeruginosa* if HIGH dose and prolonged infusion
  - Failed vs ESBL producing *Enterobacterales* as compared to meropenem (Merino trial)
- Better than ampicillin-sulbactam for empiric therapy due to 50% resistance of *E.coli*

2022 PREVIEW QUESTION

ARQ #1

- A 63 y.o. male has COVID-19 pneumonia with a BAL-documented super-infection due to *E.coli*.
- The *E.coli* is reported resistant in vitro to ceftriaxone, cefazolin, and aztreonam.

2022 PREVIEW QUESTION

AR ? #1

- The *E.coli* is likely ESBL positive and is susceptible in vitro to the following drugs. Which drug is preferable for specific therapy ?
  - A. Doripenem
  - B. Tobramycin
  - C. Meropenem
  - D. Imipenem-cilastatin-relebactam
  - E. Piperacillin-tazobactam

MERINO Trial: P/T vs Mero for *E.coli, K.pneumoniae* ESBL Producers

- Design: PRDB.* 72 hrs from pos.culture to enroll; 30 minute infusions of Pip/tazo.
- 30 day all cause mortality:
  - Piperacillin-tazobactam: 12.3 %
  - Meropenem: 3.7 %
- Other Issues:
  - Breakpoints/inoculum effect for P/T
  - Co-production of ESBL and oxacillinase?
- Three confirmatory controlled trials in progress

* PRDB=Prospective Randomized Double-Blind

Comparison of activity of Piperacillin-tazo. Vs Ampicillin-sulbactam

Target Bacteria	Ampicillin-sulbactam	Piperacillin-tazobactam
E.coli	+/-	++
Aeromonas sp.	+/-	+
Klebsiella sp.	+	+
ESBL producing E.coli; Klebsiella sp.	0	+/- or 0
Citrobacter, Morganella, Providencia sp.	0	+
Pseudomonas aeruginosa	0	+ (dose dependent)
Anaerobic GNB (*B.fragilis*)	+	+
In short: Prefer Pip/tazo for empiric therapy.		

Ampicillin-Sulbactam

Use as a source of sulbactam in combination therapy of MDR *Acinetobacter species*

- **Dose for sulbactam component for Acinetobacter* : 4 hr IV infusion of 9 gm of Amp-Sulb (6 gm Amp +3 gm Sulb) q8h**

European J of Pharm. Sci. 2019; 136:104940

Piperacillin-tazobactam: AEs

- **Common to All beta-lactams:**
  - **Allergy, seizures, neutropenia, thrombocytopenia**
  - **Drug-drug interactions: Rare**
- **Pip-tazo AE issues:**
  - **Sodium overload--36-90 meq of sodium in a full daily dose ; can aggravate CHF management**
  - **Pseudo-enhancement of vancomycin-induced nephrotoxicity with P/T + V**

Cephalosporin "Generations"

Generation	Spectrum	Comment
First (Cefazolin)	*MSSA; E.coli, Kleb.sp.*	No activity versus enterococci
Second(Cefoxitin, Cefotetan)	Original target *Bacteroides fragilis*	*B.fragilis* resistance increasing
Third(Ceftriaxone[ctx])	Most of the aerobic GNBs: Enterobacterales	"Extended spectrum"
Fourth (Ceftazidime; Cefepime)	Antipseudomonal	Cefepime not porin dependent
Fifth (Ceftaroline)	Like CTX + MRSA	No activity vs. enterococci
Sixth (Ceftolozane/Tazo)	ESBL producing GNBs; Also antipseudomonal	No activity Vs. *Bacteroides* species
Seventh (Ceftaz/Avibactam)	(ESBL producing GNBs) & KPCs	Inconsistent activity vs *Bacteroides species*

Cephalosporin "Generations"

Generation	Spectrum	Comment
Eighth: Cefiderocol	Serine/Metallo Carbapenemase producing Enterobacterales and Non-fermenters*	No useful activity vs Gram positives and anaerobic bacteria

- *Non-fermenters: *Acinetobacter sp. ,Burkholderia sp., Ps.aeruginosa,*
- *Stenotrophomonas maltophilia*

What you need to know about GNB producing ESBLs:

- **Phenotypic Detection by micro. lab based on:**
  - **Detected by In vitro "R" to penicillin, cefazolin, ceftriaxone, ceftazidime, azreonam (see Dr. Patel's lecture)**
  - **Partial reversal of "R" by BLIs (Clav/Tazo)**
  - **Similar Resistance Pattern Could be due to:(Decreased permeation + Efflux pump) or AmpC production**
- **Preferred therapy: Meropenem**
  - **Alternative: Ceftolozane-tazobactam, Cefepime (if low MIC)**
  - **Others: Plazomicin, FQs +/-, Polymyxins**
  - **Avoid Piperacillin-tazobactam**

Oral Carbapenem-Sparing Antibiotics for ESBL Producing Bacteria Causing Uncomplicated Cystitis

- **F**osfomycin
- **A**moxicillin-clavulanate
- **N**itrofurantoin

From IDSA Guidance on treatment of antimicrobial resistant gram-negative bacilli, 9/8/20. https://www.idsociety.org/practice-guideline/amr-guidance

ARQ #2

- A 45 y.o. female has a chronic Foley catheter for neurogenic bladder as a result of trauma-induced paraplegia.
- H/O multiple episodes of symptomatic cystitis and/or pyelonephritis.
- Admitted with fever, nausea and vomiting and requiring pressors and fluids for hypotension. She has no drug allergies.

ARQ #2

- After culture of blood and urine, empiric therapy with ceftazidime.
- Within a few hours, the blood culture is reported positive for *Enterobacter cloacae*

ARQ 2

- Which one of the following would you recommend ?
  - A. Pending phenotypic susceptibility, continue ceftazidime
  - B. No need to wait, de-escalate now to ceftriaxone
  - C. Switch to empiric ceftolozane-tazobactam
  - D. Switch to empiric ceftaroline

AmpC enzymes hydrolyse all cephalosporins except: ceftolozane/tazo, ceftaz/avi, and cefiderocol

- Comes two ways:
  - Gene On plasmid, constitutive synthesis, easy to detect resistance in vitro
    - Found in *E.coli and Klebsiella species*
  - Gene In chromosome of KEC:
    - K: *Klebsiella(Enterobacter) aerogenes*
    - *E: Enterobacter cloacae*
    - *C: Citrobacter freundii*
    - In high % of KEC, AmpC is repressed

Chromosomal AmpC Genes

- Need exposure to a cephalosporin for de-repression of AmpC gene; Initial isolate may test susceptible to early generation cephalosporins
- KEC bacteria most frequently involved.
- Due to rarity, have dropped rest of the SPACE/SPICE acronyms

Bottom Line on AmpC

- If presence of a KEC organism, even if susceptible in vitro, Avoid treatment with all cepholosporins except Ceftolozane/tazo, ceftaz/avi, or cefiderocol
- Empiric therapy of a KEC organism infection: Ceftolozane/tazo or Meropenem
- Avoid piperacillin-tazobactam

ARQ 3

2022 PREVIEW QUESTION

- Which one of the following would you recommend as therapy for a "difficult to treat resistant" *Pseudomonas aeruginosa* outside of the urinary track ?
  - A. Meropenem-vaborbactam
  - B. Ceftolozane-tazobactam
  - C. Cefepime
  - D. Ceftazidime
  - E. Ertapenem

ARQ #4

- 60 y.o. female smoker, admitted, intubated, and ventilated due to severe COPD with Acute Respiratory Failure.
- Chest X-Ray: New bibasilar infiltrates and Emphysema
- Empiric ceftriaxone and azithromycin
- Sputum positive for both rhinovirus and *Klebsiella pneumoniae* resistant to both ceftriaxone and azithromycin
- Also "Resistant" to: all fluoroquinolones, aminoglycosides, pip/tazo, and all carbapenems

ARQ #4

- Which one of the following antibiotics is most likely to have activity vs. this likely KPC infection ?
  - A. Tigecycline
  - B. Ceftazidime-avibactam
  - C. Aztreonam
  - D. Ceftolozane-tazobactam

Cefiderocol

- First cephalosporin stable in presence of GNB producing metallo-beta-lactamases
- PI: "For complicated UTI due to susceptible GNB with no other treatment options"
- Spectrum of activity includes:
  - XDR Enterobacterales
  - XDR Non-fermenters (Steno, Pseudo, Acineto)
  - No activity vs gram + bacteria or anaerobic bacteria

Cefiderocol Warning

- Found an increase in all cause mortality in patients Rx with cefiderocol (24.8%) vs BAT (18.4%) in critically ill patients with infection due to carbapenem resistant GNB.
- See package insert for warning and details

Testable Cephalosporin AEs

- **Cross Allergenicity: Ceftazidime, Cefiderocol, and Aztreonam have same side chain**
- **Ceftriaxone: Crystals in Biliary tree (Pseudo-cholelithiasis)**
- **Cefepime: Non-convulsive status epilepticus**
- **No Drug-Drug interactions**

Carbapenem Family

Carbapenem	Comment(s)
Imipenem-cilastatin	Avoid in meningitis patients: seizure potential
Meropenem	Less potential for inducing seizures
Ertapenem	Not active vs *Ps.aeruginosa and other non-fermenters*; Once daily therapy
Doripenem	⇧mortality vs Imipenem in VAP trial
Meropenem-vaborbactam and Imipenem-cilastatin-relebactam	Active vs Klebsiella producing carbapenemases (KPCs); Not active vs metallo or Oxa 48 carbapenemases

Carbapenems: Spectrum of antibacterial activity

Active versus:	NOT ACTIVE versus
MSSA and Enterobacterales + ESBLs	*MRSA*
*Pseudomonas aeruginosa#**	*Stenotrophomonas maltophilia*
Bacteroides fragilis	*Acinetobacter (variable)*
Enterococcus faecalis	*Enterococcus faecium*
Listeria monocytogenes	

 # Resistant to ertapenem.

***Resistance can emerge during therapy via porin closure and efflux pumps**

AZTREONAM (monobactam)

- **Only beta-lactam with NO activity vs. Gram positive bacteria: e.g., *S. pneumoniae***
  - **Safe with IgE mediated Pen/Ceph.allergy & aerobic GNB infection; cross allergenicity with ceftazidime**
- **The In vitro resistance of GNB is a phenotypic marker for production of ESBLamases**
  - **Has In vitro activity vs GNB that produce metallo-carbapenemases; however, inactivated by concomitant production of ESBLs**
    - **Use Ceftazidime-avibactam plus aztreonam to treat GNB co-producing ESBL and metallo-Carbapenemase**
    - **Reference: Clin. Inf. Dis. 2021; 72: 1871**

IN SUMMARY: Beta-Lactams

- **ESBL production: Meropenem**
  - **Ceftolozane-tazo. backup**
- **For risk of inducible AmpC production : Meropenem (Ceftolozane-tazo backup)**
- **Serine-based Carbapenemase (KPCs): Ceftazidime –avibactam, Meropenem-vaborbactam, or Imipenem-cilastatin-relebactam**
- **Metallo-based carbapenemase production: Ceftazidime-avi + Aztreonam**

Fluoroquinolones (FQs)

- **Family: Ciprofloxacin, Levofloxacin, Moxifloxacin, Delafloxacin**
- **The GOOD: Broad Spectrum of Activity, Large volume of distribution, High oral bioavailability**
- **The BAD: Increasing "R", Serious AEs(C.diff.) Many Drug-Drug interactions; FDA Safety Warning.**
  - **Conclusions:**
    - **Uncomplicated infections(bronchitis)---AVOID**
    - **Severe infections--- weigh RISK vs Benefit**

FQ Pharmacology

- **Parenteral:**
  - **Higher doses for *Ps.aeruginoa***
  - **Excreted in urine**
  - **High concentrations in prostate gland**
- **Oral:**
  - **Bioavailability of 59-95%**
  - **Chelation by multi-valent cations decreases bioavailibility:**
    - **Calcium**
    - **Iron**
    - **Zinc, Magnesium, Aluminum**

Preferred FQs vs: ?

- **For aerobic GNB: Ciprofloxacin**
- **For *Pseudomonas aeruginosa*: Ciprofloxacin**
- **For respiratory pathogens: Levofloxacin, delafloxacin , and Moxifloxacin**
- **For Anaerobic bacteria: Moxifloxacin**
- **For Mycobacteria: Moxifloxacin**
- **For MRSA : Delafloxacin**

Resistance ("R") to FQs

- **FQ Antibacterial activity due to blockade of DNA replication via binding to DNA Gyrase and Topoisomerase enzymes**
- **Multiple mech. Of "R":**
  - **Mutations of enzyme targets**
  - **Efflux pumps, altered cell wall permeation**
  - **Target protective proteins, drug acetylation**
- **Frequent Concomitant "R" of GNB to beta-lactams via:**
  - **Production of ESBLs**
  - **Production of Carbapenemases**

FQs and *Clostridioides difficile*

- **Most common drug class to cause *C.difficile colitis***
- **Second are the cephalosporins**
- **Third is clindamycin**

FQs and Acute Liver Injury

- **Compared to clarithromycin, there is an increased risk for acute liver injury within 30 days of prescription use of moxifloxacin or levofloxacin (ORs 2.2 and 1.85)**
- **No identified increased risk after use of ciprofloxacin**

QTc Prolongation: Potential Risk with all FQs except Delafloxacin

- **>500 msec., or > 60 msec prolongation from baseline, increases risk of torsades de pointes & ventricular fibrillation.**
- **Low serum K and/or Mg ; Concomitant drugs increase risk: e.g., mefloquine, haldol, fosphenytoin.**
- **None of FQs are high risk used alone; problem: concomitant drugs (cytochrome P-450 inhibition) and/or electrolyte abnormalities.**
  - **Moxifloxacin: Highest association; Delafloxacin the lowest.**

FQ Drug-Drug Interactions

- Cipro inhibition of cytochrome P450 resulting in impaired elimination of other drugs
- NSAIDs plus FQs displace GABA from GABA receptors: Lowers seizure threshold
- Rifampin and rifapentine lower serum level of moxifloxacin; of import for combined therapy of Mycobacteria

FQs and Chelation-Related AEs

- Aortic aneurysm and aortic dissection
- Tendinopathy (Tendon rupture)
  - OR 8.3 if over age 60 and
  - OR 9.1 if using oral steroid
- Arthropathy

Aminoglycoside Family

- Amikacin
- Gentamicin
- Streptomycin
- Plazomicin
- Tobramycin

AG: Spectrum of Activity

- Active vs.:
  - Aerobic gram-negative bacteria
  - Typical and atypical mycobacteria
  - Variable: *Ps.aeruginosa, S. aureus* X 24 hrs
- No activity vs.:
  - Gram-positive cocci: e.g., *S.pneumoniae*
  - Anaerobic bacteria
  - Non-fermenters: *Acinetobacter sp., Stenotrophomonas maltophilia*
- Often part of combination therapy
- Monotherapy vs Tularemia and Plague

AG: Mech. of Action & "R"

- Binds to 30s ribosome; Concentration-dependent Bactericidal activity
- Multiple mechanisms of resistance:
  - Most Frequent
    - Enzymatic alteration of drug: adenyl., acetyl., phosporyl.
      - Plazomicin is least susceptible to enzymatic attack
    - Methylation of ribosomal binding site
  - Less Common
    - Efflux pump
    - Porin closure
- Bacteria "R" to beta-lactams & FQs often have concomitant "R" to AGs

AG: Pharmacology

- Basis of once daily dosing:
  - Concentration dependent cidal activity coupled with
  - Long post-antibiotic effect
- Result is improved antibacterial activity and less risk of toxicity
- EXCEPTION: Combination therapy of enterococcal endocarditis requires TID low dose AG therapy

AG: Shared Adverse Effects

- Nephrotoxicity: Acute tubular necrosis
- Ototoxicity:
  - Cochlear (genetic predisposition & non-reversible)
  - Vestibular (irreversible but host can compensate)
- Neuromuscular blockade (neomycin)

Metronidazole

- Antibacterial and anti-protozoan activity requires a strict anaerobic environment
- "Gold Standard" for treatment of *Bacteroides species*
  - Other Drugs active vs *B.fragilis*: Pip/tazo, Amp/sulb, Carbapenems, Erava/Omadacycline
- Other clinical Indications: Bacterial vaginosis, Amebiasis, Giardiasis, and *Trichomonas vaginitis, part of combo therapy of H.pylori*
- Metro. "R" Anaerobes: *P. (Cutibacterium) acnes, Peptostreptococci, Eikenella* and *Actinomyces*

Metronidazole: Adverse Effects

- Metallic taste; "furry" tongue
- Disulfiram (Antabuse) reaction (N/V, flushing, tachycardia, dyspnea) after alcohol use
- Prolonged use: peripheral, autonomic , and/or optic neuropathy
- Aseptic meningitis
- After 3 weeks: confusion and cerebellar dysfunction

Is the patient's encepalopathy due to your antibiotic therapy ?

Antibiotic	Time to onset	Syndrome
Beta-Lactams	Within days *	Seizures; abnormal EEG
FQs, Macrolides	Within days	Delusions/Hallucination; normal MRI
Metronidazole	Weeks	Cerebellar dysfunction with abnormal MRI

* High serum concentrations due to renal insufficiency
Reference: Neurology 2016; 86:963

What do you need to know ?

- **In the USA there are roughly 210 FDA-approved antibacterials**
- **As of 2020, there are 43 anti-bacterials in the clinical development pipeline***
- **What do you need to know for the certifying examination ?**

*** WHO;2021. License: CC BY-NC-SA 3.0 | GO**

Main Points

- **Based on relative safety and efficacy, prefer beta-lactam antibiotics**
- **Due to adverse effects, Aminoglycosides, Fluoroquinolones, and Polymyxins are often in an alternative role**
- **Selection of preferred therapy is based on many variables----not just the MIC**
- **Due to complexity of resistant genotypes, need phenotypic antibiotic resistance testing**

Genotypic Resistance: Pro and Con

- **Pro: May allow customized choice of antibacterial therapy that may result in improved safety and efficacy with less promotion of resistance**
- **Con:**
  - **Gene presence does not necessarily equal gene activity**
  - **At present, not widely available, slower than phenotype**
  - **Expensive**

1. **The new antibiotic pipeline is at a low ebb which increases the import of antibiotic stewardship.**
2. **Increasing antibiotic resistance is an existential threat.**
3. **Stewardship requires decreased use of empiric antibiotic therapy and an increase in specific/directed antibiotic therapy.**

IDSA AMR Guidance – Sep 20, Nov 21, 2021

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

Published by IDSA, 9/8/2020

A Focus on Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy

IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 2.0

Published by IDSA, 11/22/2021

A focus on AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* Infections

Pranita D. Tamma*, Samuel L. Aitken, Robert A. Bonomo, Amy J. Mathers, David van Duin, Cornelius J. Clancy

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

07 – Core Concepts: Antibacterial Drugs II Gram Negative Organisms
08 – Antibacterial Drugs II: Key Points and Questions That Could Be on The Exam

Speaker: David Gilbert, MD

IDSA Guidances on the Treatment of Antimicrobial-Resistant Gram-Negative Infections: Version 1.0 and 2.0

Focus on infections caused by:

1.0

- **ESBL-E: Production of ESBLs by *Enterobacterales***
- **CRE: Carbapenem Resistant *Enterobacterales***
- **DTR-*P. aeruginosa: Difficult to treat P.aeruginosa***

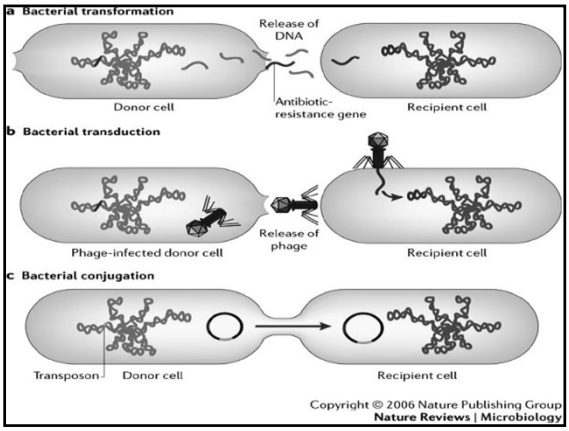
2.0

- **AmpC-E: AmpC producing *Enterobacterales***
- **CRAB: Carbapenem resistant *Acinetobacter baumannii***
- ***Stenotrophomonas maltophilia***

Nov, 2021, https://www./

Overview

- **First Lecture: Beta-lactams, FQs, AGs, Metronidazole**
- **A second on line lecture to finish review of antibacterials used for infections due to Gram-negative bacteria: Polymyxins, Nitrofurantoin, Fosfomycin, Tetracyclines, TMP/SMX**
- **Dr. Boucher will discuss antibiotics primarily active vs Gram-Positive bacteria**



If choice of treatment is based on comparative risk of adverse effect between a beta – lactam antibiotic and other antibiotic classes active vs Aerobic GNBs,

The best answer is usually the BETA-Lactam !

Beta-Lactam Efficacy associated with time above MIC

- **For Exam, pick regimen with prolonged or continuous infusion**
- **Supportive data for prolonged/continuous infusion for multiple beta-lactams:e.g.,**
  - **Ampicillin-sulbactam**
  - **Cefazolin**
  - **Cefepime**
  - **Ceftazidime**
  - **Doripenem**
  - **Meropenem**
  - **Piperacillin-tazobactam**
  - **Vancomycin**

Ref.: Sanford Guide to Antimicrobial Therapy, 2021

The Major Families of Carbapenemases

Non-Metallo (Serine at active site)	Metallo (Zinc at active site)
KPC (Class A)	VIM (Class B)
OXA-48 et al (Class D)	New Dehli Metallo-Blasé (Class B)
	IMP (Class B)

KPC=Klebsiella-producing carbapenemases; OXA=oxacillinase; IMP=Imipenemase; VIM=Verona integron-encoded metallo Blamase; NDM= New Dehli metallo BLamase

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FQs and Neurologic AEs

- Altered mental status
- Peripheral neuropathy
- Seizure
- Pseudotumor cerebri
- Exacerbation of myasthenia gravis

Drugs with predictive activity vs over 80% of *B. fragilis* isolates ?

Beta-lactams

- Amoxicillin-clav.
- Ampicillin-sulbactam
- Piperacillin-tazo.
- Ceftolozane-tazo
- All 6 FDA approved carbapenems
- TOTAL of 10

Non-Beta-lactams

- Metronidazole/Tinidazole
- Delafloxacin/Moxifloxacin
- Chloramphenicol
- Eravacycline
- Omadacycline
- Total of 5-7

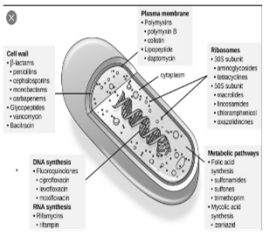
Beta-Lactam Treatment of Carbapenemase Producing GNBs

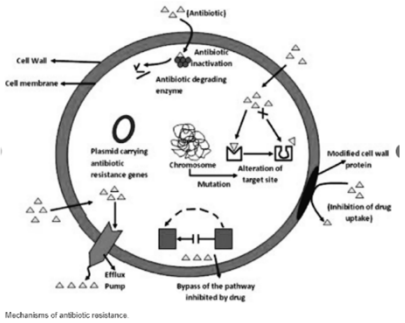
- Class A (KPCs-Klebsiella-Producing Carbapenemases):
  - Ceftazidime-avibactam
  - Meropenem-vaborbactam; Imipenem-cilistatin-relebactam
  - Cefiderocol
- Class B (Metallo-carbapenemases):
  - Ceftazidime-avibactam + Aztreonam
  - Cefiderocol
- Class D (OXA-type) carbapenemases (heterogeneous and low level enzymatic hydrolysis)
  - May not hydrolyse ceftazidime and cefepime
  - Ceftazidime –avibactam active (Avibactam binds OXA-48).
  - Reference: AAC 2021;65: e00184-21

What do you need to know ?

- Major mechanisms of antibacterial activity
- Spectrum of antibacterial activity
- Mechanisms and "language" of antibacterial resistance
- Drug Pharmacology: PK/PD, Distribution, Drug-drug interactions, Excretion, Unique toxicities (Allergy lecture to follow)
- Pertinent Clinical Microbiology (see Dr. Patel's lecture): Phenotypic patterns of resistance to beta-lactams
- Useful acronyms: SPACE-M, KPCs, NDM-CP, PEACHES

Mechanisms of Action of Antibacterials





Mechanisms of antibiotic resistance.

How do bacteria acquire genes that control resistance mechanisms?

- **Transduction via bacteriophages (bacterial viruses): species specific**
- **Transformation: scavenge and incorporate naked DNA of dead bacteria**
- **Conjugation: cytoplasmic bridges between species with transfer of plasmids**
- **Spontaneous mutations**

What is a plasmid?

- **Extra chromosomal circular DNA**
- **Can replicate independent of chromosomal DNA**
- **Replication can be constitutive or induced**
- **Exchanged between species by conjugation**
- **Can carry genes for multiple antibacterial resistance determinants and virulence factors**

What is a transposon?

- **Mobile short stretch of DNA**
- **Can move between different points within a genome by a process termed transposition.**
- **Not capable of self-replication**

What is an integron?

- **Collects genes from transposons and forms chunks of DNA called cassettes**
- **Integrons allow transposons/cassettes to move from chromosome to plasmid DNA .**
- **Then the plasmid DNA can spread via conjugation from one genus to another.**
- **Mobile genetic elements= plasmids, transposons, integrons**

Conjugative Plasmids

- **Increasingly common**
- **Carry multiple resistance genes expressed in vitro as resistance to beta-lactams, FQs, Aminoglycosides, other drugs.**

Beta-Lactam – Beta-Lactamase Inhibitor (BLI) Combinations

- **The six current BLIs are: Clavulanic acid, Tazobactam, Sulbactam, Avibactam,Relebactam, and Sulbactam . Not All are beta-lactams.**
- **BLIs demonstrate irreversible ("suicide") binding to bacterial beta-lactamases**
- **To date, there are 3 BLIs combined with a penicillin, 1 combined with a cephalosporin, and 2 combined with a carbapenem.**
- **Sulbactam is the only BLI with clinically useful antibacterial activity: active vs. Acinetobacter sp.**

Summary: Vanco:P/T as of 2020

- Vancomycin is potentially nephrotoxic
- Piperacillin-tazobactam alone has a very low potential to cause nephrotoxicity
- The reported increased ACUTE KIDNEY INJURY with V + P/T is at least partly due to the blockade of the renal tubular secretion of creatinine by piperacillin
- Current evidence would suggest that the combination of V+P/T is no more nephrotoxic than Vancomycin alone

Ceftriaxone "R" *E. coli*

- 25% "R" of organisms in the order *Enterobacterale* worldwide; In Asia, 50% of *E.coli* are resistant to ceftriaxone
- Most common mechanisms of resistance:
  - 1. Production of Extended spectrum beta-lactamase (ESBLs)
  - 2. If *Enterobacter species*: could be Production of Amp C cephalosporinase
  - Carbapenems effective in presence of both mechanisms
- Are there any carbapenem sparing cephalosporins ?

Collateral Damage from Carbapenem Therapy for ESBLs

- Selection of CP "R" strains of Enterobacterales, and/or Non-Fermenters (e.g., *Acinetobacter sp.*)
- Selection of vanco "R" enterococci, MRSA, Candida species
- Nonetheless, based on the MERINO trial, Meropenem is Drug of Choice for treatement of ESBL producing Enterobacteraceae

FDA Approved Beta-Lactam Beta-Lactamase Inhibitor Combinations

Penicillins	Cephalosporins	Carbapenems
Amoxicillin-clavulanate	Ceftolozane-tazobactam	Meropenem-vaborbactam
Ampicillin – sulbactam	Ceftazidime-avibactam*	Imipenem-cilastatin-relebactam
Piperacillin-tazobactam		

Note: so far 6 Beta-lactam inhibitors and none inhibit class B metallo-carbapenemases

* Only avibactam inhibits chromosomally-mediated AmpC ESBLs

ARQ #2

- 40 y.o. surgeon has surgical repair of torn anterior cruciate ligament of his knee. Single dose of cefazolin as prophylactic antibiotic.
- Three days later: Purulent knee exudate. GNB on gram stain. Ceftriaxone (CTX) started empirically
- At five days: Growing *Klebsiella* (*Enterobacter) aerogenes* suscept. To CTX
- At Ten days: Knee still inflamed. Repeat culture: *K.(E.) aerogenes* resistant to CTX

ARQ #2

- Which one of the following is the most likely explanation of the *Klebsiella*(*E.) aerogenes* resistance to ceftriaxone ?
  - A. Mutation in Cephalosporin cell wall binding protein
  - B. Activation of a Cephalosporin efflux pump
  - C. Activation of an inducible chromosomal cephalosporinase
  - D. Expression of constitutive plasmid cephalosporinase

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Cefiderocol

- Clinical studies:
  - Microbial eradication: Imipenem 56% ; Cefiderocol 73%
  - Day 14 mortality: Best available therapy 12 %; Cefiderochol 25%
- Has catechol side chain that utilizes iron transport system (siderophore). "Trojan horse"
- No serious AE , so far: GI 2-4%, C.difficile, Seizures
- For salvage therapy when no other option available

Aztreonam Activity vs Carbapenemase-Producing GNB

Active versus:	NOT active versus:
Metallo-Carbapenemases (Gp B)	Klebsiella-producing Carbapenemases (KPCs)(Gps A & D)
Enterobacterales(if no ESBLs)	ESBL producers
Pseudomonas aeruginosa	*Acinetobacter; Stenotrophomonas*

*"Difficult to Rx" Resistance of Ps.aeruginosa **

Preferred Therapy	Alternative Therapy
Ceftolozane-tazobactam	Aminoglycoside monotherapy (Gentamicin, Plazomicin et al)
Ceftazidime-avibactam	
Imipenem-cilastatin-relebactam	
Cefiderocol	
In addition, need Source Control	

*DTRx defined as "R" to Pip/tazo, ceftazidime, cefepime, Aztreonam, Meropenem, Imipenem-cilastatin, and FQs.

Reference: IDSA 2020 Guideline on Rx of Antimicrobial Resistant Gram-Negative Infections: CID 2021;72: 1109

Primary & Alternative Rx of ESBL and Carbapenemase Producing Enterobacterales*

Resistant	Sensitive	Presumed Mechanism	Primary Treatment	Alternative Treatment
CTX & Aztreonam	Mero, P/T, Ceftolo-Tazo	ESBL**	Mero: Extended Infusion	Ceftolo-tazo, FQ, TMP/SMX
Ertapenem	Meropenem	Serine Carba-penemase	Meropenem	Ceftz-Avi
Erta + Mero	Ceftz-Avi	Serine Carbapenemase	Ceftaz –Avi	Mero-vaborbactam ; Imipenem-relabactam
Ceftaz-Avi, Cpenems, azithromycin	Cefiderocol, Plazomicin, Polymyxin	Metallo (Zn) Carba-penemase	Ceftaz-Avi + Aztreonam	Cefiderocol; Eravacycyline if IAI

*IDSA Guideline:CID 2021;72:1109; **If chromosomal, not detected until induced

Fluoroquinolones

- Broad spectrum synthetic bactericidal antibiotics that inhibit DNA synthesis of both intracellular and extracellular bacteria
- Increasing antibacterial resistance
- Increasing recognition of serious adverse events
- Benefit needs to exceed risk

If I say Amp C, you think:All cephs destroyed except ceftolozane-tazobactam or ceftazidime/avibactam.

Bacteria with Amp C Genes come 2 ways:

Chromosomal & Inducible

- M: *Morganella*
- *Y: Yersinia*
- *S: Serratia*
- *P:*
- *Pseudo/Proteus/Provid.*
- *A: Aeromonas/Acinetobact.*
- *C: Citrobacter*
- *E: Enterobacter species* (19%)

On plasmid; constitutive

- *Escherichia coli*
- *Klebsiella species*

Treatment: Carbapenem. Maybe Pip/Tazo.; Beware of cefepime with MIC of 4 -8.
AAC 2015;59:7558
JAC 2016;71:296

Microlab cannot detect unless induced by treatment. !!!!

09

Core Concepts: Antifungal Drugs

Dr. John Bennett

09 – Core Concepts Antifungal Drugs

Speaker: John Bennett, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antifungal Drugs

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7/12/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclosures Off-Label Use

- **Will be cited as discussed**

Plan of the talk

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

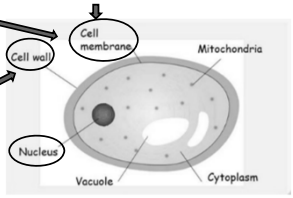
Antifungal drugs

Amphotericin makes cell membrane leak

Azoles stops sterol synthesis for the cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Flucytosine blocks DNA synthesis in nucleus



DRUG RESISTANCE IN FUNGI: BLOCK TARGET ENZYME

1. ASPERGILLUS AND CANDIDA: AZOLE RESISTANCE IN CYP51A

- gene CYP51A ← modified CYP51A =drug resistance

Lanosterol → C14-demethylase → ergosterol in cell membrane

Azole

2. CANDIDA : ECHINOCANDIN RESISTANCE IN FKS1, FKS2

genes FKS1 and FKS2 ← modified gene=drug resistance

Substrates → glucan synthase → glucan fibers in cell wall

Echinocandin

Antifungal resistant species

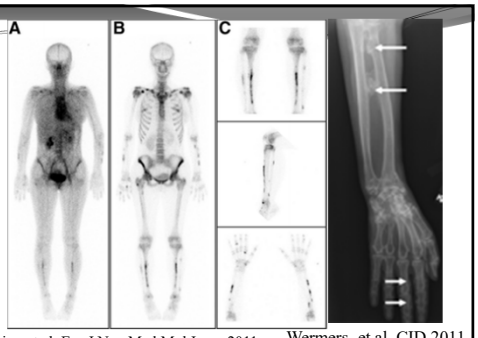
- Amphotericin B resistant: Scedosporium apiospermum (Pseudallescheria boydii), Aspergillus terreus, Variable in Candida lusitaniae, C. auris
- Fluconazole resistant: All moulds, Candida krusei, Candida auris, Candida haemulonii, some Candida glabrata
- Voriconazole resistant: mucormycosis, uncommon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

Azole antifungals

Voriconazole: the fundamentals

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

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



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

Isavuconazonium/Isavuconazole

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

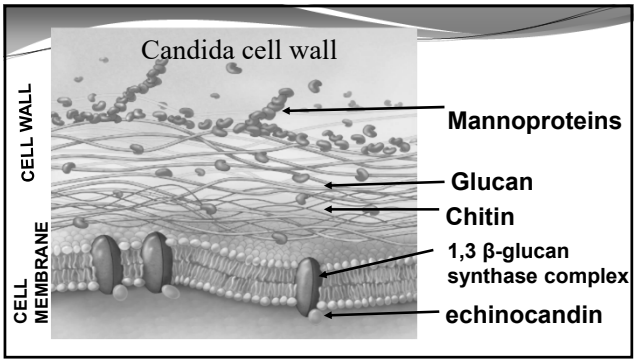
Posaconazole

- Approved for prophylaxis in GVHD or prolonged neutropenia. Aspergillosis good data, not approved.
- Extended release three 100 mg tablets twice first day then daily. IV same dose, has cyclodextran. 7-10 days for steady state. Check trough levels (usually 1-5 mcg/ml)
- Has been used in mucormycosis once patient has responded to amphotericin B
- Interactions with CYP3A4 increase some drug levels
- Well tolerated. Hypertension, hypokalemia

FLUCONAZOLE

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

Echinocandins



Caspofungin, Micafungin, Anidulafungin

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

Clinical trials in deeply invasive candidiasis

Treatment candidemia)
Caspofungin, micafungin, anidulafungin effective

Isavuconazole "not noninferior" to caspofungin in candidemia (don't use)

Prophylaxis for candidiasis: trials in micafungin (neutropenia), fluconazole (HSCT), posaconazole (HSCT)

Caspofungin and Micafungin in invasive aspergillosis

- IDSA Guidelines: "Primary therapy with an echinocandin is **NOT** recommended.
- Prophylaxis for aspergillosis: micafungin best studied, most often used, not FDA approved

Flucytosine

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

Now for a few questions

Question #1

A 47-year-old male with known HIV, poorly compliant with ARV, last CD4 20/mcl, presents with low grade fever and headache. Blood culture is growing a yeast, not yet identified. Starting micafungin would be a poor choice if the isolate is which of the following:

a. A. Candida parapsilosis
b. B. Cryptococcus gattii
c. C. Candida auris
d. D. Candida krusei
e. E. Candida glabrata

Question #2

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

Question #2 Continued

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

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

INFECTIOUS DISEASE BOARD REVIEW AUGUST 30–31 2022 PREVIEW QUESTION

Question #3

Echinocandin class of antifungals has which mechanism of action:

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

Question #4

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

Question #4 Continued

Which of the following would be most appropriate?

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

Question #5

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

Question #5 Continued

According to the IDSA guidelines and literature you recommend:

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

PREVIEW QUESTION

Question #6

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

PREVIEW QUESTION

Question #6 Continued

The most probable cause was:

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

Question #7

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

Question #7 Continued

Which of the following would be preferred?

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

Question #8

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

Question #8 Continued

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

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

Take home messages

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

Take home, continued

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

New approved antifungals

Otesaconazole (Vivjoa, CT-1161) Oral drug for recurrent vulvovaginal candidiasis in *women not of reproductive potential or breast feeding.* Teratogenic. Take weekly 3 months persists ca. 2 years . Trials for onychomycosis

Ibrexafungerp (Brexafemme) Oral drug for refractory vulvovaginal candidiasis. 2 tabs. $572. Echinocandin-like

Investigational antifungals in clinical trials

- **Olorofim**. Novel drug for Aspergillus, cocci, rare molds (not Mucorales or yeast). PO
- **Rezafungin**. IV once weekly echinocandin.
- **Fosmanogepix**. Novel drug for Candida, Aspergillus, rare molds (not Mucorales). PO, IV
- **Encochleated amphotericin B**: PO. low absorption.

The End

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10

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

Dr. Camille Kotton

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

Speaker: Camille Kotton, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

Camille Nelson Kotton MD, FAST, FIDSA
Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group, Infectious Diseases Division, Massachusetts General Hospital
Associate Professor, Harvard Medical School

7/21/2022

Disclosures of Financial Relationships with Relevant Commercial Interests

Company	Role	Details
Biotest	Consultant	Scientific advisory board, medical education (CMV immunoglobulins)
Hookipa	Consultant	CMV Vaccine trial
Merck	Consultant	Clinical trial adjudication, scientific advisory board (CMV)
Oxford Immunotec	Consultant	Scientific advisory board (CMV), medical education (TB)
Takeda	Consultant	Clinical trial adjudication, scientific advisory board (CMV)

Human Herpesviruses Family

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

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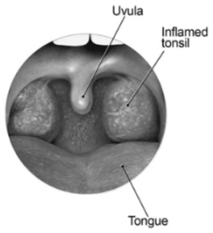
"Mononucleosis Syndrome"

- Clinical Features:
  - Fever
  - Malaise
  - Myalgias, arthralgias
  - Pharyngitis
  - Lymphadenopathy
  - Hepatomegaly / splenomegaly
- Laboratory Findings:
  - Lymphocytosis (>50%; >4500/mm3)
  - Atypical lymphocytes (>10%)
  - Abnormal LFTs



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Differential Features of Most Common Causes of Mononucleosis Syndrome

	EBV	CMV	Toxo	HIV
Fever	++++	++++	++	++++
Myalgias / Arthralgias	++	+++	+	+++
Lymphadenopathy	++++	+	++++	+++
Sore throat	++++	++	+	+++
Exudative pharyngitis	++++	+	0	0
Headache	+++	++	+	++
Rash	+	+	+	+++
Splenomegaly	+++	++	+	++
Hepatomegaly	+	++	+	0
Atypical lymphocytes	++++	+++	+	++
Elevated LFTs	++++	+++	0	+

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Differential Diagnosis of Pharyngitis

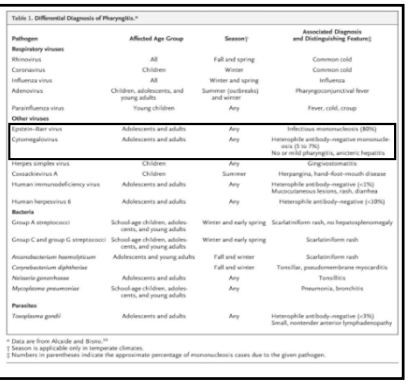
Table 1. Differential Diagnosis of Pharyngitis.*

Pathogen	Affected Age Group	Season†	Associated Diagnosis and Distinguishing Feature‡
Respiratory viruses			
Rhinovirus	All	Fall and spring	Common cold
Coronavirus	Children	Winter	Common cold
Influenza virus	All	Winter and spring	Influenza
Adenovirus	Children, adolescents, and young adults	Summer (outbreaks) and winter	Pharyngoconjunctival fever
Parainfluenza virus	Young children	Any	Fever, cold, croup
Other viruses			
Epstein–Barr virus	Adolescents and adults	Any	Infectious mononucleosis (80%)
Cytomegalovirus	Adolescents and adults	Any	Heterophile antibody–negative mononucleosis (5 to 7%); No or mild pharyngitis, anicteric hepatitis
Herpes simplex virus	Children	Any	Gingivostomatitis
Coxsackievirus A	Children	Summer	Herpangina, hand–foot–mouth disease
Human immunodeficiency virus	Adolescents and adults	Any	Heterophile antibody–negative (<1%); Mucocutaneous lesions, rash, diarrhea
Human herpesvirus 6	Adolescents and adults	Any	Heterophile antibody–negative (<10%)
Bacteria			
Group A streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash, no hepatosplenomegaly
Group C and group G streptococci	School-age children, adolescents, and young adults	Winter and early spring	Scarlatiniform rash
Arcanobacterium haemolyticum	Adolescents and young adults	Fall and winter	Scarlatiniform rash
Corynebacterium diphtheriae		Fall and winter	Tonsillar, pseudomembrane myocarditis
Neisseria gonorrhoeae	Adolescents and adults	Any	Tonsillitis
Mycoplasma pneumoniae	School-age children, adolescents, and young adults	Any	Pneumonia, bronchitis
Parasites			
Toxoplasma gondii	Adolescents and adults	Any	Heterophile antibody–negative (<3%); Small, nontender anterior lymphadenopathy

* Data are from Alcaide and Bisno.[2]
† Season is applicable only in temperate climates.
‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

Luzuriaga K, Sullivan JL. N Engl J Med 2010;362:1993-2000.

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

Speaker: Camille Kotton, MD

Non-ID causes of mononucleosis syndrome with atypical lymphocytosis

- Drug hypersensitivity syndrome
- Can be induced by several drugs:
  - anticonvulsants such as **phenytoin, carbamazepine**
  - antibiotics such as **isoniazid, minocycline**

Epstein Barr Virus

Epstein Barr Virus: Epidemiology

- Majority of infections are asymptomatic in early childhood
- Adolescent seroprevalence:
  - Resource limited regions >95%
  - Higher resource regions ~40-50%
- Primary infection in adolescents or adults results in ~50% symptomatic dz (infectious mononucleosis)
- 500 cases/100,000 population/year in USA
  - incidence rate for those 15--19yo estimated 200 – 800 cases per 100,000
- Occasionally transmitted by transfusion or organ/stem cell transplant
- Latently infected memory B lymphocytes serve as lifelong viral reservoirs
  - EBV is capable of transforming B lymphocytes, resulting in malignancy

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Epstein-Barr virus Mononucleosis

- Transmission - saliva (due to prolonged shedding for months), sexual
- Long incubation period – 4 to 8 weeks
- Clinical – viral prodrome with **fever**, malaise, headache
  - **Pharyngitis** with tonsillar exudate
  - Symmetrical cervical **adenopathy**, posterior > anterior
  - Palatal petechiae, periorbital edema, and rash (maculopapular, urticarial, or petechial)
  - Splenomegaly in 15 to 65% of cases
  - Acute symptoms persist 1-2 weeks, fatigue can last for months
- Lab - lymphocytosis with atypical lymphocytes
- Diagnosis - serologic. Non-specific heterophile Ab ("monospot"); specific Ab (VCA, EBNA)
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine
- EBV reactivation mostly asymptomatic

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Complications of Primary EBV Infection/Infectious Mononucleosis

General:

- Splenic rupture in 0.5-1%, male > female, mostly w/in 3 weeks (up to 7 weeks)

****avoid contact sports for 4 weeks minimum****

- Prolonged fatigue/malaise (>6 mo. in 10%)
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess
- Airway obstruction from massive adenopathy

Heme syndromes:

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

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Neurologic Complications of Primary EBV Infection/Infectious Mononucleosis (1 to 5% of cases)

- Viral meningitis
- Encephalitis
- Optic neuritis
- Transverse myelitis
- Facial nerve palsies
- Guillain–Barre syndrome
- Acute cerebral ataxia
- Hemiplegia
- Sleep disorders
- Psychoses

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

Speaker: Camille Kotton, MD

Laboratory Findings in EBV Infectious Mononucleosis

- CBC - elevated lymphocytes, often >50%
- Atypical lymphocytes = range 10-90% (manual differential only)
  - >=10% atypical lymphocytes in a pharyngitis patient --> sensitivity of 75% and specificity of 92% for the diagnosis of infectious mononucleosis (Ebell MH Am Fam Physician 2004)
- Total white blood cell count averages 12,000 to 18,000/microL
- Elevated liver function tests
  - AST, ALT (90%), alkaline phosphatase (60%)
  - Elevated bilirubin less common (45%, but jaundice in <10%)
- EBV viral load/PCR - *not necessary for routine mononucleosis*, may be useful in transplant or other immunocompromised patients

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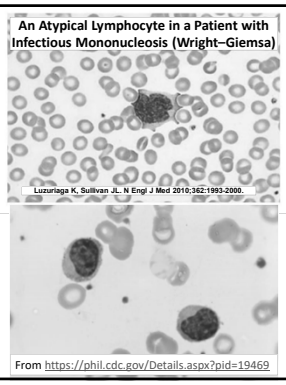
An Atypical Lymphocyte in a Patient with Infectious Mononucleosis (Wright–Giemsa)



From https://phil.cdc.gov/Details.aspx?pid=19469

Atypical lymphocytes

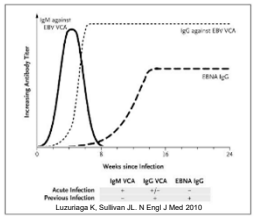
- Large pleomorphic, non-malignant peripheral blood lymphocytes
- **CD8+ cytotoxic T cells** activated by exposure to viruses (e.g., CMV, EBV, HIV, etc.) or other antigens (e.g., toxo)

General features:

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

EBV Serology

- **Viral capsid antigen (VCA)**
  - Anti-VCA IgM appears early in EBV infection then disappears in 4-6 weeks
  - Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then **persists for the rest of a person's life**.
- **EBV nuclear antigen (EBNA)**
  Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly **appears two to four months after onset of symptoms and persists for the rest of a person's life.**
- **Early antigen (EA)**
  Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.
- **Monospot test**
  The Monospot test is not recommended for general use, poorly sensitive/specific. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis.
- The antibody response occurs rapidly during primary EBV infection



Luzuriaga K, Sullivan JL. N Engl J Med 2010

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

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

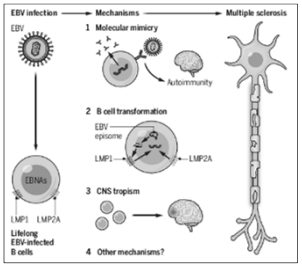
Kjetil Bjornevik[1†], Marianna Cortese[1†], Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[4], Stephen J. Elledge[9], David W. Niebuhr[10], Ann I. Scher[4], Kassandra L. Munger[1‡], Alberto Ascherio[1,11,12‡]

Science 375, 296–301 (2022)

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

My interpretation:

- Interesting observation
- Nothing for us to do clinically, no antiviral treatments
- EBV vaccine may be helpful in the future



Model for multiple sclerosis development

From Robinson & Steinman, Science, Jan 2022 Vol 375 Issue 6578

EBV after Solid Organ Transplantation

- High risk for EBV syndromes and proceeding to post-transplant lymphoproliferative disorder (PTLD), especially if donor seropositive/recipient seronegative (D+R-)
  - Best to monitor periodically for the first two years after transplant
- If EBV viremia, reduce immune suppression whenever possible
- No evidence that any current antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

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

Question

2022 PREVIEW QUESTION

An 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.

Her heterophile antibody test (Monospot) is **negative**. In addition to other tests, you order EBV-specific serology.

Which EBV-specific antibody profile would confirm a diagnosis of acute infectious mononucleosis?

Response	VCA IgM	VCA IgG	EBNA IgG	EA IgG
A	+	+	+	+
B	+	+	-	+
C	-	+	+	+
D	-	-	+	-

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

Speaker: Camille Kotton, MD

CMV

Epidemiology of CMV Infection

- Age-specific peaks in incidence:
  - Children in USA: 10-15% infected before age 5
  - Young adults at onset of sexual activity
  - ~50% adults are CMV IgG+ (NHANES, *Bate et al, Clin Infect Dis 2010*)
- Seroprevalence of CMV correlates inversely w/ socioeconomic development
  - In low-income regions, CMV seroprevalence approaches 100%.
- Transplant:
  - Organ: highest risk is donor seropositive, recipient seronegative (D+R-)
  - Stem cell: highest risk is D-R+ (opposite)
  - Superinfection can occur (organ transplant D+R+ higher risk than D-R+)

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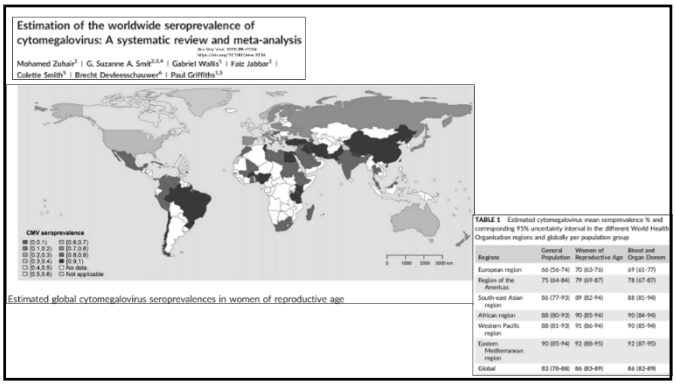

Transmission & Pathogenesis of CMV

- Beta herpesvirus
- Infection transmitted via:
  - body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - transplanted tissue (blood, organs, stem cell transplant)
    - Reduced with routine use of blood filtered/WBC-depleted
- Primary infection usually asymptomatic/subclinical
  - Mononucleosis syndrome in <10%
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses.
  - Ongoing shed is important factor in transmission
- No vaccine available; several under development

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CMV Mononucleosis Syndrome

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

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CMV: Congenital infection

- Leading cause of nonhereditary sensorineural hearing loss
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in developed countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk of congenital infection
  - Having children in daycare is major risk
  - Infants more likely to have symptoms at birth & long-term sequelae
- Reactivation maternal CMV infection - 0.9-1.5% risk of congenital infection
- Hearing loss similar in both primary and reactivation cohorts
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%

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

Speaker: Camille Kotton, MD

Cytomegalovirus: the troll of transplantation

Balfour HH, Jr. Arch Intern Med. 1979;139(3):279-80

Remember the tale of "The Three Billy Goats Gruff?" The transplant patient, like the billy goats, initially is on rocky ground and wants to cross the bridge over the rushing river to greener pastures on the other side. Cytomegalovirus is the troll under the bridge, hidden in shadows and often undetectable even by the most sophisticated diagnostic techniques. As we immunosuppress patients to help them cross the bridge, the troll comes out and threatens to devour them. Like the two smaller billy goats in the story, we clinicians are passing the buck to stall for time, hopeful that in the near future our patients, armed with either a vaccine or an effective antiviral agent, will be strong enough to throw the voracious CMV troll off the bridge and back into obscurity.

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CMV INFECTION AFTER ORGAN/STEM CELL TRANSPLANT: A SPECTRUM OF DISEASE

Direct Effects

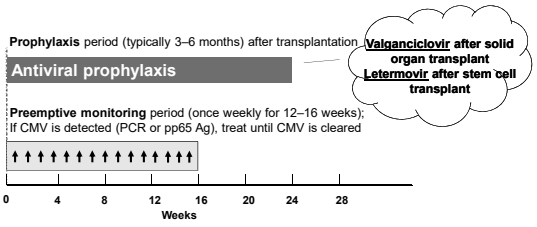
Asymptomatic Viremia

CMV Viral Syndrome
- Flu-like syndrome: fever, malaise, myalgia
- Leukopenia, thrombocytopenia

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

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

PREVENTION: Prophylaxis vs. Preemptive Therapy



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

CMV Diagnostics

- Serology
  - To diagnose acute infection, detect IgM or IgM-->IgG seroconversion
  - CMV IgG establishes donor/recipient serostatus/risk in transplantation (no IgM)
  - Serology has no role in diagnosis of acute infection in transplant setting
- Molecular diagnostics
  - Quantitative PCR – detects CMV DNA in blood, other fluids, tissues
    - Lower (somewhat) sensitivity of blood PCR for CMV GI disease, pneumonitis, retinitis
    - Variations between whole blood and plasma, different testing platforms – pick one and use that to trend results, don't compare across different specimen types/testing platforms
- Histopathology of biopsied tissue
  - Basophilic intranuclear inclusion bodies surrounded by a clear halo – "owl's eye" cells
  - CMV-specific immunohistochemical stains
- Viral culture
  - Specimens: BAL, GI biopsy, etc.
  - Tissue culture: slow; cytopathic effect in 3-21 days (shell vial technique is faster); expensive; sensitivity/specificity not optimal (viral shed vs true infection)

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TREATMENT for Transplant Recipients: Consensus Recommendations (Kotton et al, CMV Guidelines, Transplantation 2018)

- For initial and recurrent episodes of CMV disease, VGCV (900 mg every 12 hours) or intravenous GCV (5 mg/kg every 12 hours) are recommended as first-line treatment in adults with normal kidney
- Valganciclovir is recommended in patients with mild to moderate CMV disease
- Intravenous GCV is recommended in life-threatening & severe disease; after clinical response, intravenous GCV may be transitioned to VGCV
- In patients without concomitant rejection, reduction of immunosuppression is suggested in the following settings: severe CMV disease, inadequate clinical response, high viral loads, and cytopenia
- During the treatment phase, weekly plasma CMV DNA testing is recommended using an assay calibrated to the WHO standard (IU/ml) to monitor response. Also renal function.
- Antiviral treatment dosing should be continued for a minimum of two weeks, until clinical resolution of disease and eradication of CMV DNAemia below a specific threshold (LLOQ < 200 IU/ml) on one or two consecutive weekly samples
- Adjunctive immunoglobulin therapy is not routinely recommended

Risk Factors and Rates for Resistant Virus

Risk Factors
- **Inadequate antiviral drug dose or delivery**
- **Prolonged antiviral drug exposure**
- **Ongoing active viral replication (often seen w/ lack of prior CMV immunity D+/R-)**
- **Strongly immunosuppressive therapy**
- **Drugs with lower barrier to resistance**

Rates
- **Among solid organ recipients the usual incidence of resistance after ganciclovir therapy is 5% to 12%, but up to 18% in lung and 31% in intestinal and multivisceral organ transplant recipients**
- **Incidence of resistance is lower, in the 0% to 3% range, with 100 to 200 days of ganciclovir or valganciclovir prophylaxis in D+/R- kidney recipients (IMPACT trial, Humar AJT)**

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

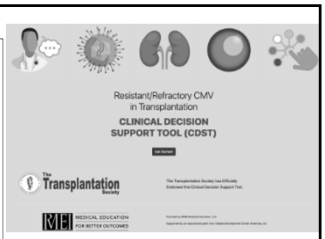
Speaker: Camille Kotton, MD

Maribavir CMV Trials Post-Transplant

Refractory CMV ± genotypic resistance (SOT & HSCT)	CMV Viremia in HSCT

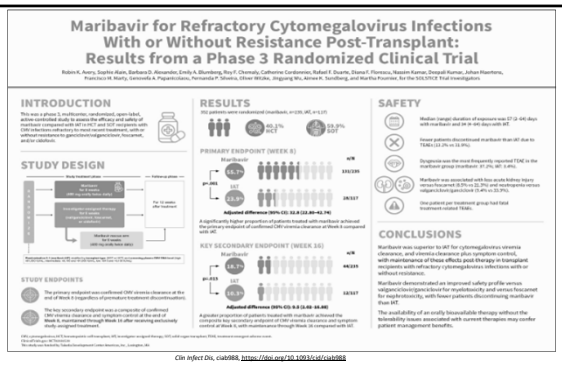
- Randomized, open-label trial of **maribavir versus standard therapy (foscarnet, cidofovir, high dose ganciclovir)** in transplant patients with resistant/refractory CMV infection
- 56% MBR vs 24% standard tx cleared CMV by end of tx at 8 weeks
- Fell to 19% vs 10% by week 16 (8 weeks after end of tx)
- Well tolerated (dysgeusia) oral drug, very $$
- ~60% of those treated w/ **maribavir or valganciclovir** cleared CMV by 3 weeks (Phase 2, Maertens et al NEJM 2019)
- Lower rates of neutropenia w/ maribavir
- Waiting on phase 3 data, FDA review

Resistant CMV Management: Guidelines



www.CDSTforCMV.com
Leads to
https://via.juxlyapps.com/pathway/archemedx/cmvsot-cdst/index.html#/disease-selection

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931.



Clin Infect Dis, ciab988, https://doi.org/10.1093/cid/ciab988

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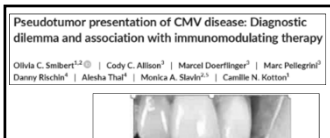

"Cytomegalo-tumor"

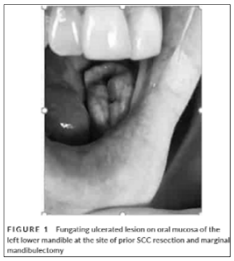

FIGURE 1 Fungating ulcerated lesion on oral mucosa of the left lower mandible at the site of prior SCC resection and marginal mandibulectomy

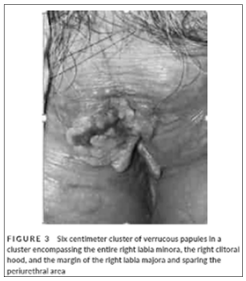

FIGURE 3 Six centimeter cluster of verrucous papules in a cluster encompassing the entire right labia minora, the right clitoral hood, and the margin of the right labia majora and sparing the perlurethral area

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

What do you recommend?

A. Could be many things – send for many different cultures and viral load testing

B. This is probably CMV – send CMV viral load testing and routine cultures, and start treatment with valganciclovir 900mg po twice a day (renally adjusted as needed) (plan if not better, will check additional diagnostics)

C. Call a transplant ID colleague for guidance

HHV-6

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

Speaker: Camille Kotton, MD

Human Herpesvirus Type 6

- Beta herpesvirus, discovered in 1986
- Two subgroups:
  - HHV-6A – uncommon pathogen, little known about clinical impact or epidemiology
  - HHV-6B – frequent infection in healthy children, etiology of roseola (exanthem subitem), & cause of reactivation disease
- Primary infection common in first year of life, >60% infected by 12 months
- Transmission by saliva; incubation period ~9 days (5-15 days)
- Replicates and establishes latency in mononuclear cells, esp. activated T-lymphocytes
- Can integrate into human germline cells (1%); chromosomally inherited, will be viral load/PCR high level positive forever; can reactivate from integrated state
- No vaccine available or under development

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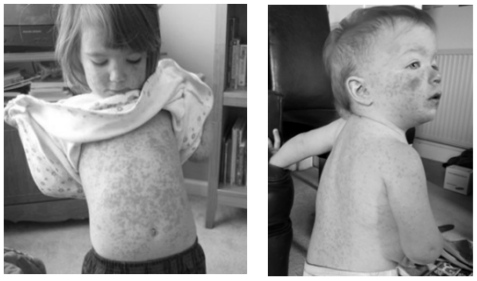
Exanthem subitum (roseola, sixth disease)



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

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Human Herpesvirus Type 6: Normal hosts

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

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HHV-6: Immunocompromised Hosts

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

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HHV-8

Human Herpesvirus Type 8

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

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

Speaker: Camille Kotton, MD

HHV-8 Associated Diseases

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

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HHV-8 Diagnosis and Treatment

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

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Human Herpes Virus Antiviral Prophylaxis & Treatment Agents

Antiviral agent	EBV	CMV	HHV-6	HHV-8	HSV	Varicella	BK	Adeno-virus
Commercially available								
acyclovir/valacyclovir/famciclovir*		high dose +/-			x	x		
ganciclovir IV/valganciclovir PO		x	x	+/-	x	x		
foscarnet**		x	x	+/-	x	x		
cidofovir**		x	x	+/-	x	x	poor	+/-
letermovir (prophylaxis only)		x						
Maribavir (treatment only)	*In vitro*	x						
Novel/investigational antiviral agents (SOT)								
brincidofovir (not available)	*x*	*x*			*x*	*x*	*x*	*x*
Pritelivir (phase III)					*x*			

Summary: EBV, CMV, HHV-6, HHV-8

- Common childhood infections
- All human herpesviruses establish latency
- Serology useful, viral load detection more helpful in immunocompromised
- Infection from donor → recipient usually major risk factor
- Varied spectrum of clinical manifestations, from infectious syndromes to malignancies (EBV, HHV-8)
- Antiviral prophylaxis/treatment – best for CMV, more limited utility for others
- No vaccines available

Questions? ckotton@mgh.Harvard.edu

MASSACHUSETTS GENERAL HOSPITAL
TRANSPLANT CENTER

11

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Dr. Kevin Winthrop

11 - Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Speaker: Kevin Winthrop, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Kevin L. Winthrop, MD, MPH
Professor, Divisions of Infectious Diseases, Public Health and Preventive Medicine
Oregon Health & Science University

7/12/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Research Grant: Insmed**
- **Consultant: Insmed, Spero, Red Hills, Paratek, AN2**

Nontuberculous Mycobacterium (NTM)

- "MOTT" or "Atypical"
- Environmental organisms
  - Soil, lakes, rivers, municipal water systems
  - Resistant to chlorine and most disinfectants
- Biofilm
  - Live within amoeba, legionella, others

Laboratory Growth Characteristics

- "Slow" growers (>2 weeks in AFB media, liquid media more quickly)
  - M. avium complex (MAC), *M. kansasii, M. marinum, M. xenopi*
- "Rapid" growers (4-7 days in routine blood agar)
  - *M. abscessus, M. chelonae, M. fortuitum*
- *"Need help" growing*
  - *M. marinum, M. haemophilum, M. ulcerans,*
  - *M. genavense (often molecular ID)*

NTM Disease Clinical Manifestations

- Pulmonary (75%)
  - MAC
  - *M. kansasii*
  - *M. xenopi*
  - *M. abscessus*
  - *M. malmoense*

NTM Disease Clinical Manifestations

Skin and Soft tissue (15%)
- MAC, *M. marinum, M. abscessus, M. chelonae, M. fortuitum, M. kansasii, M. ulcerans*

- Lymph node disease (5%)
  - *MAC, (historically also M. scrofulaceum*)

Disseminated (5%)
- MAC, *M. kansasii, M. abscessus, M. chelonae, M. haemophilum*

- Hypersensitivity pneumonitis (0%)
  - *MAC and hot-tubs*

Important Bug-Setting Associations

- Corneal Disease
  - *M. chelonae*
- Healthcare/hygiene associated outbreaks
  - *M. chelonae, M. fortuitum, M. abscessus*
- Line-associated
  - *M. mucogenicum*
- HIV setting
  - *MAC, M. kansasii, M. genavense, M. haemophilum*
- Tropical setting
  - *M. ulcerans* (buruli ulcer)

Other Pearls Based on Species

- *M. gordonae*
  - *Contaminant*
- NTM are not communicable
  - CF?
- *M. immunogenum, M. simiae*
  - Pseudo-outbreaks
- *M. szulgai*, *M. kansasii*, and *M. marinum*
  - Cross-react with IGRAs
- *M. fortuitum* lung disease
  - Aspiration
- *M. marinum*
  - Fish and fishtanks

Question #1

IDBR 2022 PREVIEW QUESTION

72 year old female with chronic cough, normal CXR, and 1/3 sputums grow MAC. Which one of the following you do recommend?

A. CT scan of chest AND Additional sputum AFB cultures
B. Empiric therapy with azithromycin, ethambutol, and rifampin
C. Additional sputum AFB cultures
D. Wait for in vitro susceptibility data and then treat.

Pulmonary NTM

2007 ATS/IDSA diagnostic criteria:

- Patient has both radiographic evidence of disease and pulmonary symptoms

AND

- At least 2 sputum cultures positive, or
- One BAL or tissue specimen with positive culture, or
- Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Griffith D et al. *AJRCCM* 2007

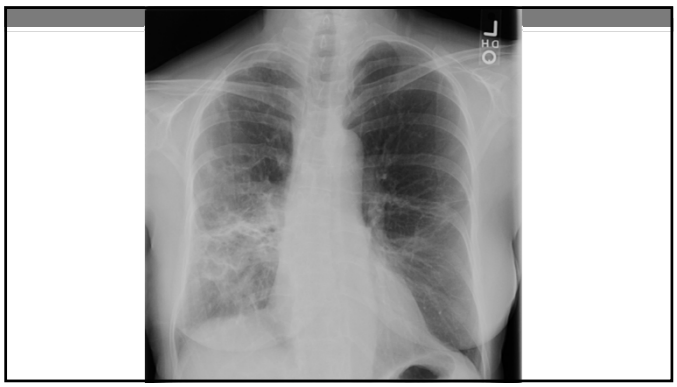
Pulmonary NTM

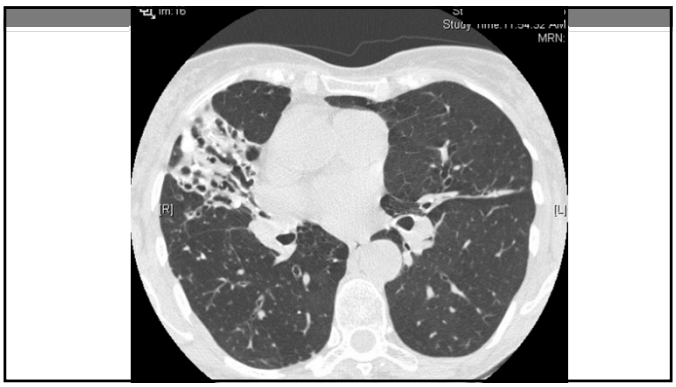
- MAC is most common etiology (60-90%)
- M. kansasii and M. abscessus
  - *M. kansasii* primarily in the South
  - Recent *M. abscessus* increase in CF
- Other organisms of importance
  - *M. xenopi* (northern US/ Canada, Europe)
  - *M. malmoense* (Europe)

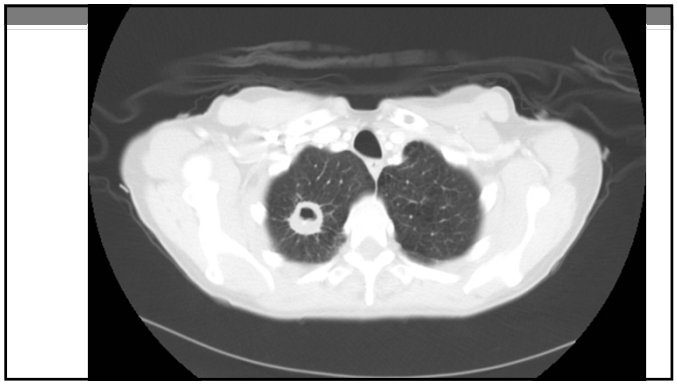
Two Types of MAC Pulmonary Diseases

- Older male, smoker, COPD
  - Apical cavitary or fibronodular disease
  - More rapidly progressive
- Older female ("Lady-Windermere")
  - Scoliosis, thin, pectus deformities*, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis ("tree and bud") on HRCT
  - Slowly progressive

***Iseman MD et al. *Am Rev Respir Dis.* 1991**







Pulmonary NTM Risk Factors

- Underlying lung architectural abnormalities
  - Bronchiectasis, CF, α-1, emphysema
  - Prior TB, GERD/aspiration
- Exposure/transmission
  - Gardening/soil, Hot tubs
- Immunosuppressives
  - Prednisone, inhaled corticosteroids, biologics

NTM Pulmonary Disease Diagnosis

- Diagnosis ≠ decision to treat
  - Observation vs. suppression vs. cure

MAC Therapeutic Options

- Treatment best defined for MAC
  - Start Macrolide, rifampin, ethambutol
  - Amikacin first 1-2 months for cavitary disease
  - Treatment duration 18-24 months (12 month culture negative)
  - Macrolide monotherapy is contraindicated
  - Recommended to test susceptibility for macrolide
  - TIW okay if non-cavitary or not re-infection

Pulmonary M. kansasii Therapy

- *M. kansasii* clinically more like TB
  - Thin-walled cavities, upper lobes
  - Treatment with INH, RIF, EMB
  - TIW therapy ok
  - Treatment duration: 12 months culture negativity
  - High treatment success rates (90%+)
  - RIF is key drug.

Pulmonary M. abscessus ssp. Therapy

- *M. boletti, M. massiliense, M. abscessus*
  - Inducible macrolide resistance--erm (41) gene
- "Cure" = rare
- Can be more rapidly progressive than MAC
- 3-4 drugs for 18-24 months
  - 4-6 months "induction" phase
  - "suppressive strategy" thereafter

M. abscessus Therapy

- Parenteral agents
  - Omadacycline 100mg QD, Tigecycline 50mg QD, Cefoxitin 2gm TID, Imipenem 1000mg BID, Amikacin 10mg/kg TIW
- Oral agents
  - Clofazimine 50-100mg QD, Linezolid 600mg QD, moxifloxacin 400mg QD (rarely suscep), Azithromycin 250mg QD (if suscep)
  - Surgical resection

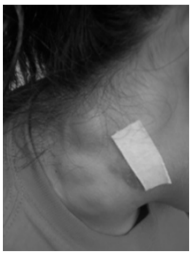
EXTRAPULMONARY NTM

1. Immunocompetent settings
2. Immunocompromised settings

Immunocompetent settings

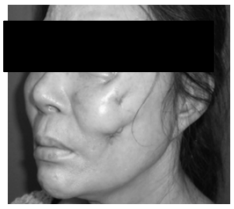
- Nail salon, trauma, surgical or injection procedures, fishtank, hot tubs
- Rapid or slow growing NTM
- Incubation period
  - Infection usually occurs 2-8 weeks after contact with contaminated water source

Children under 5 years NTM > TB



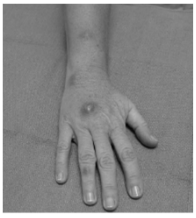
- Usually MAC
  - Males > females, age 1-2 years old
- Surgical resection alone is best therapy
- Adjunctive ABX rarely needed

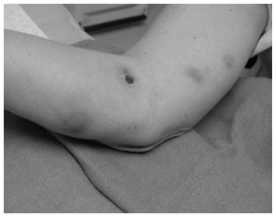
Post- plastic surgery



- Usually Rapid Grower:
  - *M. chelonae*
- Remove foreign-bodies
- Therapy as per in-vitro susceptibility
- Length 4-6 months

M. marinum---fish tank granuloma



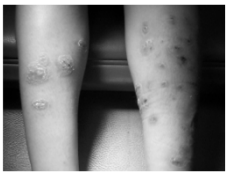


Treatment: multiple drugs

- Macrolides, sulfonamides, doxycycline, rifampin, ethambutol
- Treat with 2 agents X 3-4 months.
- Surgical debridement if necessary

Nail Salon Furunculosis

- Outbreaks and sporadic
- Rapid Growers most common (*M. fortuitum)*
- Oral antibiotics
  - 4 months fluoroquinolone and/or doxycycline
  - Can be self-limited



Tattoo-associated

- *M. chelonae*
- Tattoo-ink outbreaks
- 2-3 months oral therapy
  - Based on *in-vitro* susceptibility
  - 1-2 agents
  - Macrolides almost always

Question # 2

20 y.o. male complains of fever, night sweats and weight loss. Has generalized lymphadenopathy. HIV antibody positive; CD4 20 cells/ul. Node biopsy: non-caseating granuloma, AFB seen.

Question # 2

Based on the most likely diagnosis, which of the following do you recommend :

A. Start MAC therapy
B. Start HAART plus MAC prophylaxis
C. Start MAC therapy and HAART
D. Start HAART only

NTM in HIV

- Disseminated MAC
- GI route of infection
- Less frequent in HAART era
- Related issues
  - Clofazimine = increases mortality?
  - Rifabutin dose adjustment with PI
  - Immune reconstitution inflammatory syndrome (IRIS)

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISSEMINATED *Mycobacterium avium* IN HIV-INFECTED PATIENTS

Preferred (A, I)*	Alternative (B, I)*
Treatment	
Clarithromycin 500 mg orally twice daily + Ethambutol 15 mg/kg orally daily ± Rifabutin† 300 mg orally daily	Azithromycin 500 mg daily + Ethambutol 15 mg/kg daily ± Rifabutin† 300–450 mg orally daily
Prevention‡	
Azithromycin 1,200 mg orally weekly	Clarithromycin 500 mg orally twice daily or Rifabutin† 300 mg orally daily

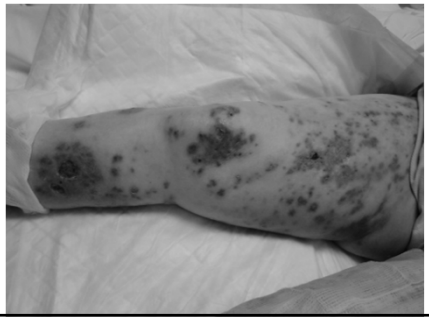
* For evidence quality, see Table 1.
† Rifabutin dose may need to be modified based on drug–drug interactions (see text).
‡ Preventive therapy indicated for persons with < 50 $CD4^+$ cells/μl; may stop if > 100 cells/μl.

Griffith D et al. AJRCCM 2007

Immunosuppression other than HIV

- Most frequently disseminated
  - Local inoculation versus GI route
- Risk factors and conditions
- ESRD, prednisone, biologic immunosuppressives
- Cancer, transplant, leukemia (hairy cell)
- Auto-antibody and cytokine/receptor deficiency states
  - INF-gamma, IL12-23 pathway, STAT-1
- Disease split between RGM and slow growers
  - RGM more common here than in pulmonary disease

M. chelonae in cancer patient



M. chelonae and *M. fortuitum* treatment

- *M. chelonae*
  - Macrolides,flouroquinolone, linezolid
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline
  - Note: tobramycin is best for *M. chelonae*
- *M. fortuitum*
  - Macrolides, flourquinolone, bactrim, doxy (50%)
  - IV drugs include aminoglycosides, imipenem, cefoxitin, tigecycline

Length of treatment for disseminated infection
3 drugs (including 1 IV) X 4-6 months
Depends on immunosuppression reversal

M. chimaera

- Slow growing. M. avium complex
  - Pulmonary disease
- Requires molecular identification
- Extrapulmonary disease
  - 150+ cases from open heart surgery: prosthetic valve, vascular graft, LVAD, heart transplant
- Aerosol from contaminated heater-cooler units used in operating room for cardiac by-pass.
- Time to diagnosis 1.7-3.6 years post-op, with cases reported up to 6 years postoperatively.
- Mycobacterial blood cultures
- Treatment: forever?

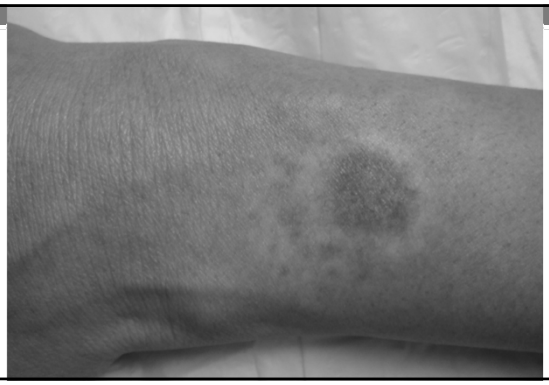
Hansen's Disease (Leprosy)

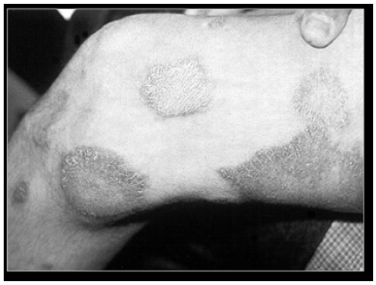
- Rare in US (100-200 cases per year)
  - Armadillos and gulf region
  - Rest imported
- Most humans resistant
  - Household contacts at risk (low risk)
  - Nasopharyngeal transmission?
- *M. leprae* does not grow in culture

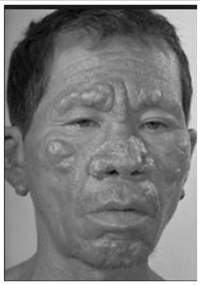
Leprosy Disease Classification

- Paucibacillary (PB)
- Most common form
  - *"Tuberculoid"*
  - Bacillary load < 1 million
  - Skin biopsy: AFB negative
  - ≤5 skin lesions

- Multibacillary (MB)
  - *"Lepromatous"*
  - Massive bacillary load
  - Skin biopsy: Floridly positive for AFB
  - >5 skin lesions.







Leprosy Treatment

- PB (6 months)
  - Dapsone 100mg daily
  - *Rifampin 600mg once monthly
- MB (12+ months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

Complications: reversal reactions, erythema nodosum
Treat with prednisone, thalidomide, other

Top 10 or 12 NTM pearls for the Boards

- Footbaths = *M. fortuitum* or other RGM
- *Plastic Surgery* = *M. chelonae* or other RGM
- Equitorial Africa = *M. ulcerans*
- HIV disseminated MAC that doesn't grow = think of *M. genavense*
- *M. abscessus* usually has inducible macrolide resistance (erm gene)
- Macrolide, EMB, RIF for 18-24 months for pulmonary MAC
- *M. gordonae* is 99.9% a contaminant
- ATS/IDSA pulmonary case definition: need one BAL or two sputums or tissue
- Know NTM species that cross-react with TB IGRAs
- No clofazimine in HIV related MAC
- *M. kansasii* behaves like TB---responds to TB drugs (RIF, EMB, INH)
- PZA not useful for any NTM

12

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

Dr. Rajesh Gandhi

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

Speaker: Rajesh Gandhi, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

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

7/6/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Scientific Advisory Board: Merck**

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

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

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

Case 1

A woman in her forties presented with 6 days of fatigue, decreased appetite, fevers and chills. She also had severe headache and myalgias.

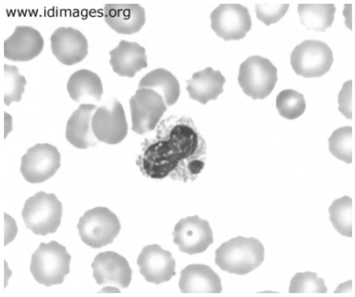
PMH: None.

SH: Patient was single and not sexually active. She denied cigarette, alcohol or illicit drug use. The patient had recently hiked in New Hampshire. She denied a history of tick bites. She had a dog but no other animal exposures.

Contributed by Anne Kasmar, M.D.

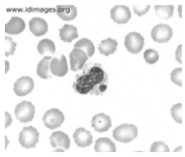
PE: She appeared well. T 103.5, BP 104/50, HR 122, RR 18, O_2 sat 97% on RA. She had no rash or adenopathy. Remainder of exam was normal.

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



Differential Diagnosis

A. Meningococcemia
B. Anaplasmosis
C. Histoplasmosis
D. Babesiosis
E. "Spotless" Rocky Mountain Spotted Fever (RMSF)



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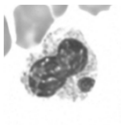
Diagnosis and Follow-up

- Peripheral blood smear showed morulae inside white blood cells, consistent with anaplasmosis.



- Diagnosis confirmed with PCR testing.
- She was treated with doxycycline; symptoms completely resolved.

8

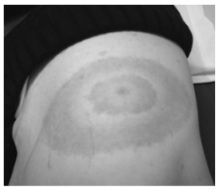
Anaplasmosis

- New England, north central states and West Coast.
- Caused by Anaplasma phagocytophilum transmitted by tick Ixodes scapularis
- Sx: fevers, chills, myalgias, headache. Rash <10%.
- Labs: leukopenia, thrombocytopenia, elevated transaminases.
- Dx: visualization of intraleukocytic bacteria (morulae) on blood smear (present in 20-80% of cases); serology (paired); serum PCR
- Treatment: doxycycline

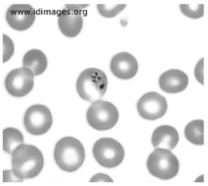
9

Rule out coinfection with Lyme, Babesia (same vector)

Lyme



Babesia



10

Differential diagnosis

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

11

Case 2

60 yo M with history of renal transplant developed multiple erythematous, raised, pruritic lesions on his thighs over the course of several weeks.

PMH: ESRD due to post-streptococcal glomerulonephritis, s/p cadaveric renal transplant in 1982; HCV infection.

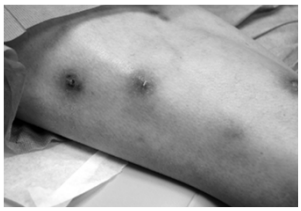
Meds: prednisone 15 mg qd; azathioprine 150 mg qd

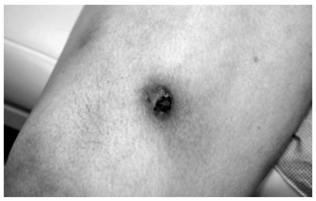
SH: Patient had healthy cat at home. Lived in rural Virginia near farm animals and frequently saw deer in his yard. Avid gardener but no recent puncture wounds. Several tick bites in the past year. Travel history: Central America 2 yrs ago.

Contributed by Raj Gandhi, M.D.

12

PE: T: 36.8. Multiple erythematous nodules on both lower extremities. Lesions were tender and non-fluctuant, some with a central necrotic area. There was no discharge. The remainder of his exam was normal.





13

Studies: WBC 3.3; Hematocrit 26%; Platelets 118,000; BUN 59 mg/dL, Creatinine 2.1 mg/dL; Bilirubin (total/direct) 2.1/1.3; AST 70; Alkaline Phosphatase 321.

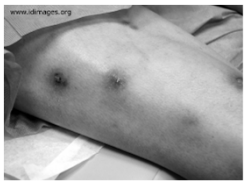
CXR: normal

Blood Cultures: no growth

14

Differential Diagnosis

1. Cryoglobulinemic vasculitis related to HCV infection
2. Nocardiosis
3. Nontuberculous mycobacteria
4. Cutaneous aspergillus
5. Botryomycosis



15

Diagnosis and Follow-up

- Patient underwent skin biopsy of a lesion on his lower extremity.
- Microscopic examination: abscess containing many polymorphonuclear leukocytes, scattered multinucleated giant cells.
- Special stains revealed acid-fast bacilli.
- Culture grew *Mycobacterium chelonae*.

16

M. chelonae

- Rapidly-growing mycobacteria
- Some strains grow best at 28-33°C
  - May account for its proclivity to cause cutaneous lesions on the extremities
- *M. chelonae* most commonly causes skin, bone and soft tissue infection
  - Disseminated cutaneous infection occurs in immunocompromised hosts, such as transplant patients and individuals on chronic steroids
  - Keratitis associated with contact lenses' wear and LASIK
  - Surgical site infection reported after cosmetic surgery, other invasive procedures

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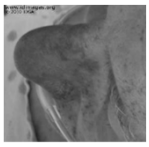
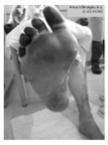
Case 3

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

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

18





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

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

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Capnocytophaga canimorsus

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

20

Differential diagnosis

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

21

Case 4

30 yo woman with HIV (CD4 cell count 20, not on therapy) presented with gradual onset of word-finding difficulties, expressive aphasia and right upper extremity weakness over 4 weeks.

SH: She lived in New England. No recent travel or known insect bites. Not sexually active.

PE: On exam, she was afebrile. She had oral thrush. She had difficulty naming objects and right-sided weakness.

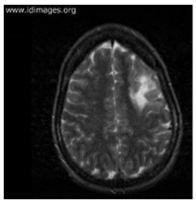
Studies: WBC count of 2.2 (44% P, 45% L)

Contributed by Wendy Yeh, M.D.

22

Her clinical syndrome is most likely caused by:

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



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

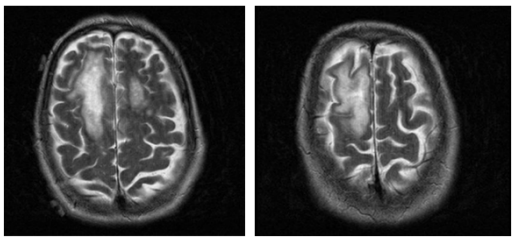
23

Progressive multifocal leukoencephalopathy

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

24

PML



Contributed by Vince Marconi, M.D.

25

Differential diagnosis

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

26

Case 5

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

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

Contributed by Rojelio Mejia, MD

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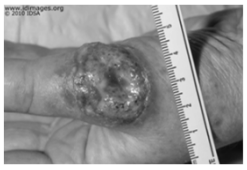
Differential Diagnosis

PE: Patient appeared well. T 98.1.
Raised ulcerated lesion on thumb with a violaceous border

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



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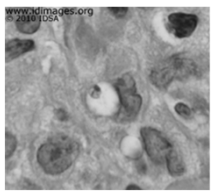
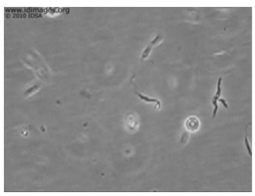
Skin biopsy showed amastigote, with kinetoplast in a vacuole. Culture of tissue from skin biopsy in Schneider's Media revealed promastigotes. PCR of tissue: *Leishmania guyanensis*.



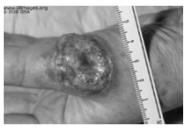
Skin biopsy, H and E stain

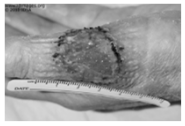


Culture of skin biopsy tissue in Schneider's medium

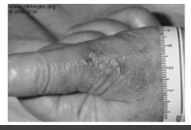
29

Treated with liposomal amphotericin





One week after treatment



Follow-up at 3 months

30

Differential Diagnosis

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

31

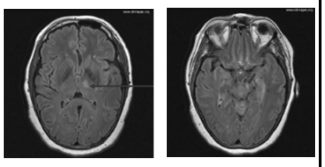
Case 6

Woman in her 50s presented with fatigue, confusion, word-finding difficulties and fever for 3 days

SH: Lived in Midwestern US. Avid outdoors person, frequently in wooded areas; husband recalls pulling a tick off her trunk recently

PE: T 101.3. Somnolent woman, oriented only to self

CSF: WBC 146 (9% N, 56% L, 35% M); RBC 14; Glc 70; Pro 109



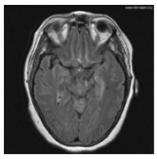
MRI: T2 hyperintensity left thalamus and substantia nigra; leptomeningeal enhancement

Contributed by Joy Chen, M.D. and Virk Abinash, M.D.

32

Differential Diagnosis

A. Neisseria meningitides meningitis
B. Herpes simplex virus encephalitis
C. Lyme meningoencephalitis
D. Powassan meningoencephalitis
E. Lymphocytic choriomeningitis



33

Diagnostic Procedures & Results

- CSF gram stain, fungal smear, bacterial and fungal cultures were negative
- CSF PCR tests for HSV, WNV, VZV, CMV negative
- CSF positive for immunoglobulin M against Powassan virus by ELISA. Confirmed at CDC

34

Powassan Encephalitis

- Transmitted by *Ixodid* ticks
- Northeast, upper Midwestern (Great Lakes) US
- Transmission period April-December
- Incubation period up to 4 weeks
- Fever, confusion, seizures, focal neurologic deficits
- CSF: lymphocytic pleocytosis
- Diagnosis:
  - MRI: T2 hyperintensity in thalamus, basal ganglia, brainstem
  - Positive IgM antibody; confirmed at CDC with PRNT

www.cdc.gov/powassan/statistics.html

35

Case 7

60 yo M presented to ED with a few hours of severe pain in right upper extremity. There was no history of trauma. Exam was normal with no obvious skin changes. He was discharged home. Over the next few hours, he developed progressive swelling of right upper extremity.

Exam: right upper extremity was diffusely swollen with a deep-red discoloration; several bullae.

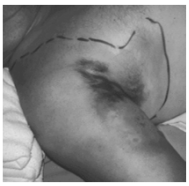
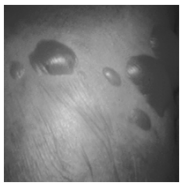
Studies: WBC 8,900 (47% polys, 38% bands). X-ray: air in soft tissues.

Contributed by Steve Calderwood, M.D.

36

Does this patient most likely have:

A. Vibrio vulnificus
B. Group A streptococcal necrotizing fasciitis
C. Mixed aerobic/anaerobic necrotizing fasciitis
D. Clostridial gas gangrene
E. Bullous pemphigoid

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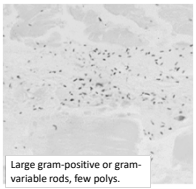
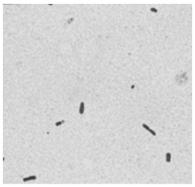
Diagnosis





Surgical cultures grew *Clostridium septicum*.

In retrospect, patient reported several month history of bright red blood per rectum. Subsequent evaluation revealed an invasive colonic carcinoma.

38

Gas Gangrene

- Traumatic gas gangrene generally due to *C. perfringens,* sometimes other Clostridial species
- Spontaneous (non-traumatic) gas gangrene most commonly due to *C. septicum*
- *C. septicum* infection associated with malignancy
  - In one series, 81% had malignancy; in 37% the cancer was occult[1]
  - Most common cancers: colorectal, hematologic.

Kornbluth et al. Medicine (1989) 68:30

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Differential Diagnosis

- **Vibrio vulnificus:** patient with liver disease, iron overload, or immunocompromising condition.
- **Group A streptococcal necrotizing fasciitis:** Would not result in air in soft tissues
- **Mixed aerobic/anaerobic necrotizing fasciiitis:** after trauma or surgery
- **Bullous pemphigoid:** Would not present in such a fulminant manner nor would gas be present in tissues.

40

Case 8

50 yo F was well until 7 days prior to admission when she noted "bite" on left thigh. Lesion enlarged over several days. Four days prior to admission, developed fatigue, arthralgias, myalgias, fever, headache. On day of admission (July), developed generalized rash on extremities, trunk, back.

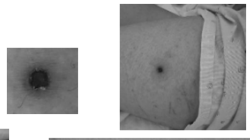
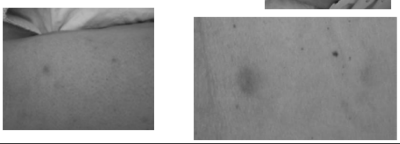
SH: Lived in New England. She had seen a mouse in her basement. She had a dog. Denied sexual activity.

PE: appeared well. T 100.5. No adenopathy. Lesion present on left thigh. Papular erythematous rash on her extremities, back, chest.

41

Does this patient most likely have:

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

42

Case 9

55 yo M was admitted with nephrolithiasis and *E. coli* urosepsis. Course was complicated by ARDS, requiring prolonged ventilatory support and a tracheostomy. On hospital day 21, he developed a nosocomial MRSA pneumonia. On hospital day 28, he developed a new fever and rash.

PMH: HTN; AF. Medications: vancomycin, nifedipine, digoxin, coumadin.

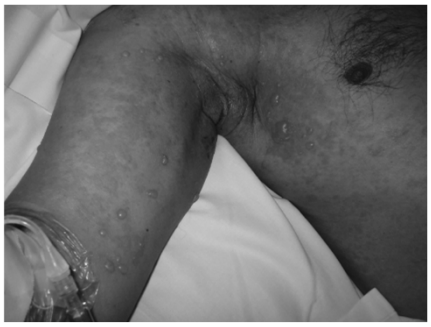
Contributor: John Beigel, M.D.

43

PE: T 103.2. Skin: erythematous areas in the axillae, back, left thigh. On this erythematous base, there were tight bullae, which expressed yellow, serous, nonpurulent fluid when opened. Exam otherwise normal.

Studies: WBC 15.7 (84% P, 9% L, 3% M, 3% E), and hematocrit 28.6%. Cultures of the bullous fluid were negative.

44



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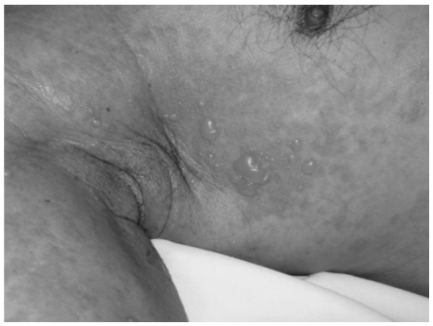
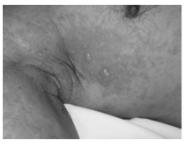


46

Differential Diagnosis

A. Dermatitis herpetiformis
B. Bullous pemphigoid
C. Linear IgA bullous disease from vancomycin
D. Herpes zoster
E. Staphylococcal scalded skin syndrome



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

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Skin and Soft Tissue Infections

Dr. Helen Boucher

13 – Skin and Soft Tissue Infections

Speaker: Helen Boucher, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Skin and Soft Tissue Infection

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

7/18/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Question #1

A 25 year old female suffers a cat bite on the forearm.

She presents one hour later for care.

If no antibacterial is administered, the percentage of such patients that get infected is:

A. **0-10 %**
B. **10-30 %**
C. **30-70 %**
D. **70-100 %**

3

Management of Animal Bites

- **Wound care: irrigation, debridement**
- **Image for fracture or as baseline for osteo or to detect foreign body ?**
- **Wound closure: NO**
- **Anticipatory (prophylactic) antibiotics**
- **Vaccines (tetanus and rabies)**

4

Cat Bites

- **30-50% cat bites become infected with bacteria**
- **Wound types: puncture**
- **Microbiology: 63% polymicrobial**
- **Infection type:**
  - **Nonpurulent wound with cellulitis, lymphangitis, or both (42%)**
  - **Purulent wound without abscess (39%)**
  - **Abscesses (19%)**

Aerobic organisms	
Pasteurella	75
Streptococcus	46
Staphylococcus	35
Neisseria ±	35
Moraxella	35
Corynebacterium	28
Enterococcus	12
Bacillus	11
Anaerobic organisms	
Fusobacterium	33
Porphyromonas	30
Bacteroides	28

Abrahamian FM1, Goldstein EJ. Microbiology of animal bite wound infections. Clin Microbiol Rev. 2011 Apr;24(2):231-46. doi: 10.1128/CMR.00041-10; *NEJM 1999; 340: 85-92*

5

Pasteurella multocida

- **In saliva of > 90% of cats and over 80% of wounds get infected**
- **Different species, *Pasturella canis*, in saliva of 50% of dogs and only 2-10% get infected**
- **Small aerobic Gram-Negative bacillus**
- **Hard to remember antibiotic susceptibility profile, but amoxicillin sensitive; alternatives can be tricky**

6

Six Pathogens That Can Cause Infection After Cat Bites

1. ***Pasteurella species***
2. **Anaerobic bacteria: e.g., *Fusobacteria***
3. ***Bartonella henselae (Cat Scratch disease)***
4. **Rabies virus**
5. ***S. aureus***
6. ***Streptococcal species***

7

Question #2

PREVIEW QUESTION

A 50 year old female with alcohol substance abuse disorder suffered a provoked dog bite

- **Bite was cleansed, tetanus toxoid given, and the dog placed under observation**
- **Patient is post-elective splenectomy for ITP; she received pneumococcal vaccine one year ago**
- **One day later, the patient is admitted to the ICU in septic shock with severe DIC and peripheral symmetric gangrene of the tips of her fingers/toes**

8

Question #2

PREVIEW QUESTION

Which one of the following is the most likely etiologic bacteria?

A. ***Pasteurella canis***
B. ***Capnocytophaga canimorsus***
C. ***Fusobacterium sp.***
D. ***Bartonella henselae***

9

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***
  - ***Susceptible to: AM/CL, PIP/Tazo, Penicillin G, and clindamycin***
  - ***Resistant to: TMP/SMX and maybe vancomycin***

10

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?

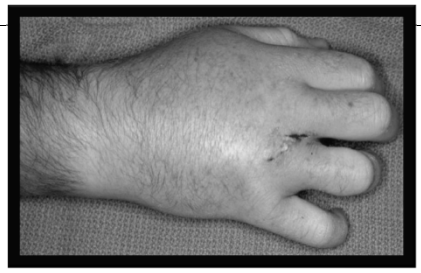
A. ***Pasteurella multocida?***
B. ***Haemophilus parainfluenza?***
C. ***Spirillum minus?***
D. ***Streptobacillus moniliformis?***

11

Rat bite fever

- **USA: *Streptobacillus moniliformis***
- **Asia: *Spirillium minus***
- **Bites or contaminated food/water**
- ***S. moniliformis*:**
  - **Fever, extremity rash**
    - **Macular/papular, pustular, petechial, purpuric**
  - **Symmetrical polyarthralgia**
- **Treatment: Penicillin or doxycycline**

12



13

Question #4

PREVIEW QUESTION

A 35 year old male suffers a clenched fist injury in a barroom brawl. He presents 18 hours later with fever and a tender, red, warm fist wound. Gram stain of bloody exudate shows a small gram-negative rod with some coccobacillary forms. The aerobic culture is positive for viridans streptococci*

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

A. ***Viridans streptococci?***
B. ***Eikenella corrodens?***
C. ***Peptostreptococcus?***
D. ***Fusobacterium species?***

***Talan, D. CID 2003; 37: 1481**

14

Question #5 (Extra Credit)

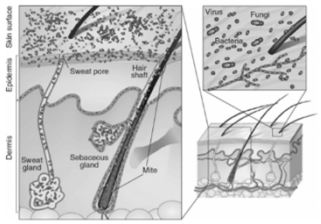
Medicinal leeches are applied to a non-healing leg ulcer.

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***

15

The Skin: Local Invasion by Structure



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

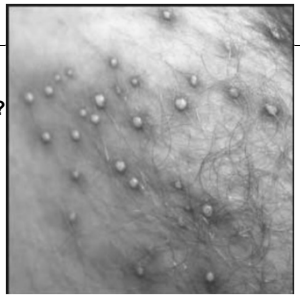
16

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**

17

What is this?

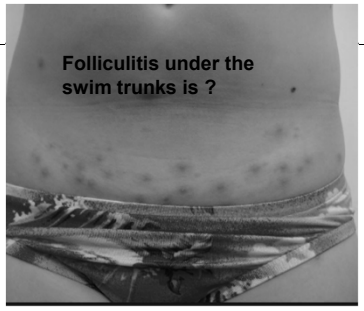


18

Superficial Folliculitis

- **Purulence (sometimes mixed with blood) where hair follicles exit skin**
- **Etiology:**
  1. ***S. aureus***
  2. ***P. aeruginosa* (hot tub)**
  3. ***C. albicans (esp. in obese patient)***
  4. ***Malassezia furfur - lipophilic yeast (former Pityrosporum sp)***
  5. **Idiopathic eosinophilic pustular folliculitis in AIDS patients**

19



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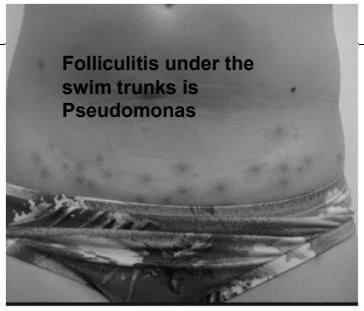


21

Microbial Etiology?

22

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.

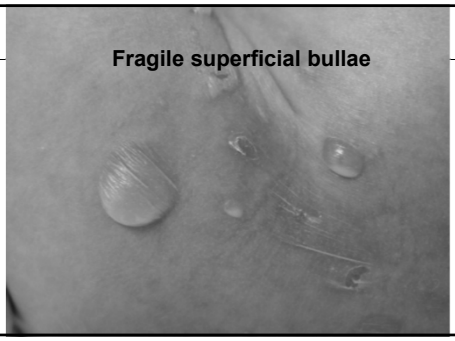
Microbial etiology

- **Streptococci: Groups A, B, C, G**

Name?

- **Streptococcal impetigo**

23



24

Fragile Bullae in Epidermis

Diagnosis?

- **Bullous impetigo**

Etiology?

- ***S. aureus***

25

Impetigo ("to attack")

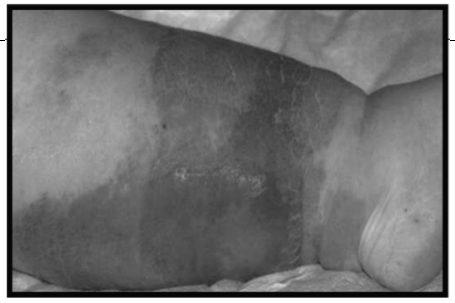
- **Bullous impetigo: *S. aureus***
- **Non-bullous impetigo: *S. pyogenes, group A***
- **So, empiric therapy aimed at *S. aureus* as could be MRSA**
- **Topical: topical antibiotic ointment (TAO), mupirocin, retapamulin**
- **Oral rarely needed**
  - **e.g, Clindamycin, doxycycline**

26

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**

27



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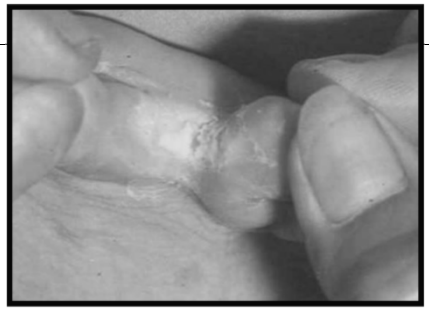


29

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis?

30

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat

NO PURULENCE

Diagnosis:

Erysipelas: Non-purulent cellulitis

31

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat.

NO PURULENCE

Diagnosis:

- Erysipelas: Non-purulent cellulitis

Etiology?

32

Acute onset of painful, rapidly spreading red plaque of inflammation involving epidermis, dermis, and subcutaneous fat. NO PURULENCE

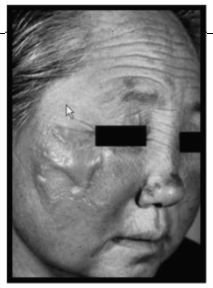
Diagnosis?

- 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*

33



34

Erysipelas ("Red Skin")

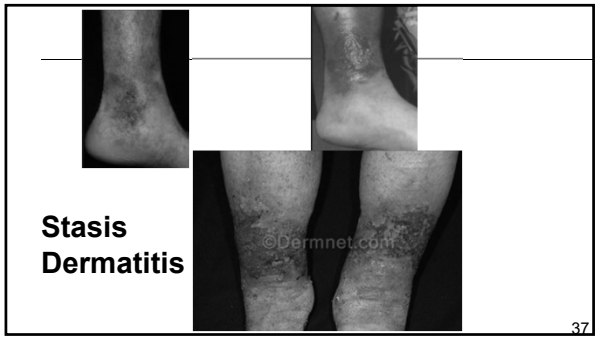
- Acute onset of painful skin, rapid progression +/- lymphangitis
- Inflamed skin elevated, red, and demarcated
- Etiology: Streptococci--Groups A,B,C, & G (*S. pyogenes, S. agalactiae, S. dysgalactiae subsp. equisimilis)*
- Predisposition:
  - —Lymphatic disruption, venous stasis

35

Erysipelas and Cultures

- Usually 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

36



37

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

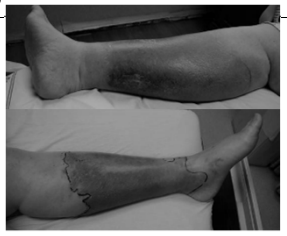
38

Treatment of Erysipelas (Non-purulent "cellulitis")

- Elevation
- Topical antifungals between toes if tinea pedis present
- Penicillin, cephalosporins, clindamycin
- Avoid macrolides and TMP/SMX due to frequency of resistance

39

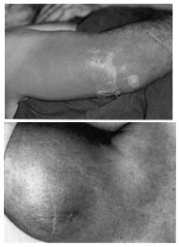
Cellulitis

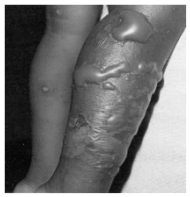


- Without localization or preceding macro or micro trauma: usually Beta strep. (usually GAS), extremities > face, elsewhere
- With localization (cut, pustule, etc.) or preceding trauma: *S. aureus*

40

Severe Cellulitis





Microbiology: Streptococci (group A>B,C,G); less often *S. aureus*; rarely GNR

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Recurrent Cellulitis

- Frequently non-group A streptococci (esp. B,G)
- Relapse > recurrence
- Prophylaxis:
  - Benzathine penicillin IM
  - Oral penicillin; other systemic antibiotics
  - Decolonization (nasal, elsewhere)

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Risk Factors for Recurrent Erysipelas

- Lower Extremity
  - Post-bypass venectomy
  - Chronic lymphedema
  - Pelvic surgery
  - Lymphadenectomy
  - Pelvic irradiation
  - Chronic dermatophytosis
- Upper Extremity
  - Post-mastectomy/node dissection
- Breast
  - Post-breast conservation surgery, biopsy

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Erysipelothrix (Gram + rod)

- On finger after cut/abrasion exposure to infected animal (swine) or fish
- Subacute erysipelas (erysipeloid)
- Severe throbbing pain
- Diagnosis: Culture of deep dermis (aspirate or biopsy)
- Treatment: Penicillin, cephalosporins, clindamycin, fluoroquinolone

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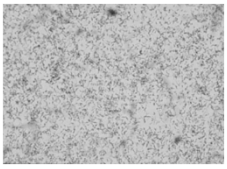
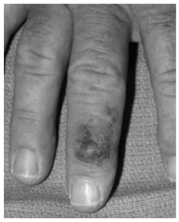
Erysipelothrix rhusiopathiae Infection



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



Resolving cellulitis caused by *Erysipelothrix rhusiopathiae*

45

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

(Continued)

46

Question #6 Continued

Which one of the following is the most likely complication of the erysipelas?

A. Bacteremic shock due *to S. pyogenes*?
B. Toxic shock due to *S. pyogenes*?
C. Bacteremic shock due to *S. aureus*?
D. Toxic shock due to *S. aureus*?

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Toxic Shock Syn. (TSS): Staph vs Strep

Feature	Staphylococcal	Streptococcal
Predisposition	Tampon, surgery; colonization	Cuts, Burns, Varicella, erysipelas
Focal Pain	No	Yes
Tissue necrosis/inflammation	Rare	Common
N/V, renal failure/DIC	Yes	Yes
Erythroderma	Very common	Less Common
Bacteremia	Very rare	60%
Mortality	<3%	30-70%

48

Sore throat and skin rash

- **20 year old man with 3 days of sore throat, fever, chills, and skin rash**
- **Rash is nonpruritic and involves abdomen, chest , back, arms ,and legs**
- **Exam: Exudative tonsillitis, strawberry tongue, rash, and tender cervical lymph nodes**

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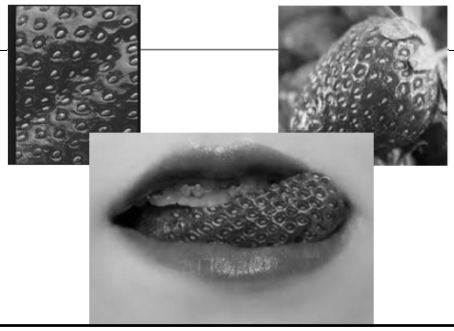

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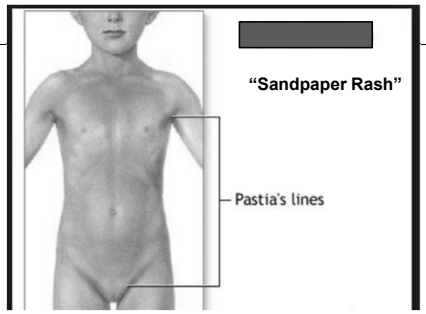

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The most likely diagnosis ?

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

52

The most likely diagnosis ?

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

53

Question 7:

- **18 year old male taking anti- seizure meds for idiopathic epilepsy develops fluctuant tender furuncle on right arm**
- **He develops fever and generalized erythroderma; wherever he is touched, a bullous lesion develops**
- **Skin biopsy shows intra-epidermal split in the skin**

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Question #7

Which one of the following is the likely etiology of the skin bullae?

A. ***S. aureus*** **scalded skin syndrome?**
B. **Bullous pemphigus?**
C. **Drug-induced Toxic epidermal necrolysis (TEN)?**
D. ***S. pyogenes*** **necrotizing fasciitis?**

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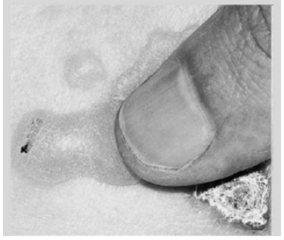
Nikolsky sign



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The Skin and Toxins of *S. aureus* and *S. pyogenes*

Organism	Toxin	Clinical Diagnosis
S.aureus colonization	TSST	TSS & Erythroderma
S. aureus colonization	Exfoliative toxin	Impetigo; scalded skin syndrome
Strep. pyogenes invasion	TSST	TSS; Erythroderma (not always)
Strep. pyogenes	Pyrogenic exotoxin	Pharyngitis; Scarlet Fever (sandpaper rash)

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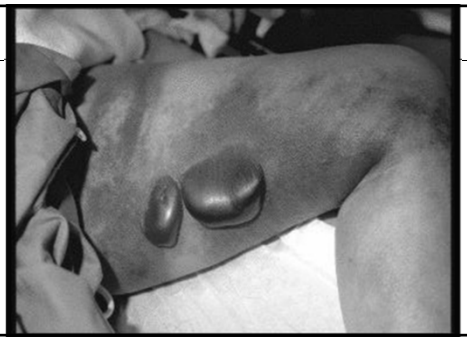

58

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

Necrotizing fasciitis is due to which one ?

a. **Streptococcal fasciitis**
b. **Staphylococcal fasciitis**
c. **Clostridial infection**
d. **Synergy between aerobe (*S.aureus, E.coli*) plus anaerobe (anaerobic strep, *Bacteroides sp*) equals Meleney's, Fournier's**

Lancet ID 2015;15:109

59

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Lancet ID 2015;15:109

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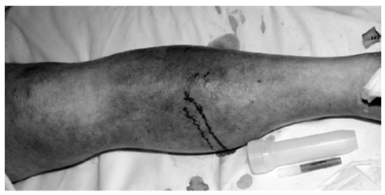
Necrotizing Fasciitis: at the bedside



Sudden onset excruciating pain & systemic toxicity
Note swelling of leg & 2 small purple bullae on anterior shin
Pressures in the anterior/lateral compartments (blood at needle entry) elevated; surgical exploration performed

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Treatment of necrotizing fasciitis

- Think of it
- Surgical debridement: sometimes several times needed to achieve source control
- Appropriate antimicrobial therapy

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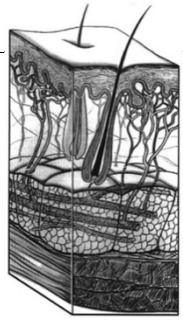

Anatomy	Syndrome
Epidermis Skin	Erysipelas Impetigo Folliculitis
Dermis	Ecthyma Furunculosis Carbunculosis
	All of this is Cellulitis
Superficial fascia Subcutaneous tissue Subcutaneous fat, Nerves, arteries, veins	Necrotizing fasciitis
Deep fascia	
Muscle	Myonecrosis (clostridial and non-clostridial)

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Question #8

A 50-year-old male african american fisherman with known cirrhosis suffers an abrasion of his leg while harvesting oysters.

Within hours, the skin is red, painful, and hemorrhagic bullae appear.

Which one of the following conditions predisposes to this infection?

A. G6PD Deficiency
B. Hemochromatosis
C. Sickle cell disease
D. Achlorhydria

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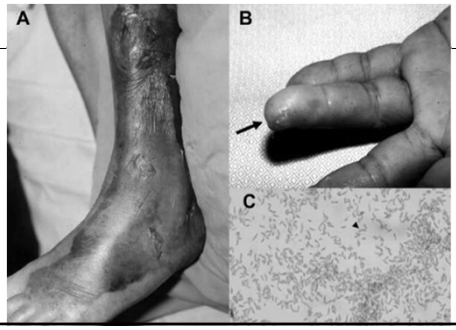

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Vibrio vulnificus

- Leading cause of shellfish(e.g., oysters)-associated deaths in USA
- Portal of entry: skin abasions or GI
- 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): doxy plus ceftriaxone (alternative is an FQ)

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Organisms Whose Growth is Stimulated by Excess Iron

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

Definition: "The sails of a ship"

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Thank You!

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

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Questions, Comments?

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- Helen.boucher@tufts.edu

Dr. Helen Boucher
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Agenda Day 2: Sunday, August 21, 2022

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

QP2

Daily Question Preview 2

Dr. John Bennett (Moderator)

QP2 – Daily Question Preview: Day 2

Moderator: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Daily Question Preview: Day 2

Moderator: Jack Bennett, MD

7/27/2022

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

2.1 **Low Dose Pathogens Commonly Cause Diarrhea Outbreaks in Day Care Center: Which of the following doesn't fit?**

A) ***Shigella***

B) ***Cryptosporidium***

C) ***Giardia***

D) ***Campylobacter jejuni***

E) Norovirus

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

2.2 **83-year-old man with bloody diarrhea develops renal failure.**

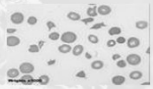
- **He has a one week history of diarrhea with stools containing blood; he undergoes colonoscopy which looks like ischemic colitis**
- **As his diarrhea improves his urine output decreases**
- **Serum creatinine is 9, platelet count of 50,000, hematocrit 20 and LDH 1,000.**

Colonoscopy Shows "Ischemic Colitis"

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

2.2

- **Stool culture on Sorbitol MacConkey Agar grows only sorbitol-fermenting *E. coli* and stool sample is positive for Shiga toxin 2 by EIA**
- **He is treated with hemodialysis**



Peripheral Smear Shows Red Cell Fragments

INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

2.2 **What is the likely cause of dysentery and renal failure in the elderly man?**

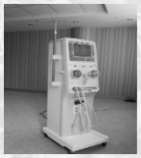
A) Ischemic bowel disease

B) Non-O157 Shigatoxin producing E. coli (STEC)

C) O157:H7 strain of STEC

D) ***Shigella dysenteriae*** **1 (Shiga bacillus)**

E) ***Campylobacter jejuni***



INFECTIOUS DISEASE BOARD REVIEW **PREVIEW QUESTION**

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

What is the likely diagnosis?

A) Scombroid

B) Paralytic shellfish poisoning

C) Ciguatera

D) Neurotoxic shellfish poisoning

E) Monosodium glutamate toxicity

QP2 – Daily Question Preview: Day 2

Moderator: John Bennett, MD

PREVIEW QUESTION

2.4 44 yr old previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache.

Cranial MRI was normal.

Lumbar CSF had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512.

Liposomal amphotericin B was begun at 5.0 mg/kg IV daily.

On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

PREVIEW QUESTION

2.4 The most important next step in this patient is which of the following:

A) Start flucytosine

B) Start fluconazole

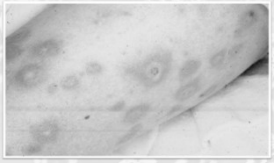
C) Start acetazolamide (Diamox)

D) Begin daily lumbar punctures

E) Start dexamethasone

PREVIEW QUESTION

2.5 35 yr old male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.



PREVIEW QUESTION

2.5 The most likely fungus is which of the following:

A) Scedosporium apiospermum (Pseudallescheria boydii)

B) Lomentospora (Scedosporium) prolificans

C) Apophysomyces elegans

D) Fusarium multiforme

E) Alternaria alternata

PREVIEW QUESTION

2.6 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 (101.1˚F), has clear lungs and benign abdomen.

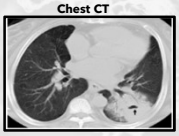
Labs reveal a normal white blood cell count, slight anemia, & normal creatinine.

PREVIEW QUESTION

2.6 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).

Chest CT



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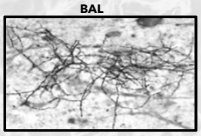


CT Image from J. Bargehr, *et al. Clinical Radiology*, 2013-05-01, Volume 68, Issue 5, Pages e266-e271.
Gram stain image from Murray, *et al.* Medical Microbiology, 7E. 2013 Saunders, Elsevier.

PREVIEW QUESTION

2.6 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

PREVIEW QUESTION

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

Exam : BP 160/40 P110, 39.5
- Rales ½ way up bilaterally
- Loud diastolic decrescendo murmur, lower left sternal border

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

A) Nafcillin

B) Vancomycin

C) Vancomycin + nafcillin

D) Vancomycin + gentamicin

E) Vancomycin + gentamicin + rifampin

PREVIEW QUESTION

2.8 A 63 y/o woman with a history of mitral valve prolapse presents with 3 weeks of low-grade fever, fatigue, generalized weakness, weight loss, arthralgias.

She is first chair violinist for the local orchestra.

Exam: BP 135/90 P100 , 38.2°C
- 3/6 holosystolic murmur, radiating the axilla
- Lungs are clear, no peripheral stigmata of endocarditis

PREVIEW QUESTION

2.8
- Serum creatinine 1.2 mg/dl
- TTE: mitral valve prolapse with 0.5 cm vegetation on anterior leaflet, moderate regurgitation
- 3/3 blood cultures from admission positive for Streptococcus mitis, penicillin MIC = 0.25 μg/ml, ceftriaxone MIC = 0.25 μg/ml.

PREVIEW QUESTION

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

A) Penicillin for 6 weeks

B) Penicillin + gentamicin for 4 weeks

C) Ceftriaxone for 4 weeks

D) Penicillin + gentamicin for 2 weeks then penicillin for 2 weeks

E) Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

PREVIEW QUESTION

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

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

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

PREVIEW QUESTION

2.9 Lab results

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

PREVIEW QUESTION

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

A) Ampicillin for 2 weeks

B) Penicillin + gentamicin for 4 weeks

C) Ampicillin + gentamicin for 4 weeks

D) Ampicillin + ceftriaxone for 6 weeks

E) Daptomycin for 8 weeks

PREVIEW QUESTION

2.10 45 year old man, one week of back pain.

He is afebrile and vital signs are normal; normal exam except for tenderness to palpation of the lower back.

MRI shows L3-L4 discitis, hyperemic marrow; 1 of 3 blood cultures is positive for coagulase-negative staphylococci.

PREVIEW QUESTION

2.10 Which one of the following would you recommend?

A) Bone biopsy with culture as the blood isolate is likely a contaminant

B) Request speciation of the blood isolate

C) PET-CT to look for another focus of infection for biopsy

D) Fungal serologies, PPD

PREVIEW QUESTION

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

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

PREVIEW QUESTION

2.11 Which one of the alternative agents would you recommend?

A) Penicillin

B) Cefazolin

C) Vancomycin

D) Daptomycin

PREVIEW QUESTION

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

The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

PREVIEW QUESTION

2.12 Which one of the following would you recommend?

A) Ceftaroline

B) Dalbavancin

C) Telavancin

D) Vancomycin

E) Linezolid

PREVIEW QUESTION

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

The best approach to the diagnosis of H. pylori infection in this patient is:

A) Immediate Hp serology

B) Immediate Hp stool antigen EIA

C) Endoscopy with rapid urease test (RUT)

D) Immediate 13C Urea Breath Test

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

PREVIEW QUESTION

2.14 Which of the following is the most appropriate next step for evaluating a 29-year-old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?

A) Stool antigen test for *H. pylori*

B) Urea breath test for *H. pylori*

C) No testing for *H. Pylori*

D) Serological testing for *H. pylori*

E) Empiric therapy for *H. pylori* regardless of testing

QP2 – Daily Question Preview: Day 2

Moderator: John Bennett, MD

PREVIEW QUESTION

2.15 The MICU attending calls you because she's noticed 4 patients with new ***Burkholderia cepacia*** complex infections in her unit over the last 6 months.

The patients were hospitalized during different periods and all were first detected >7 days after admission.

PREVIEW QUESTION

2.15 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?

14

Clinical Immunology and Host Defense

Dr. Steven Holland

14 - Clinical Immunology and Host Defense

Speaker: Steven Holland, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Clinical Immunology and Host Defense

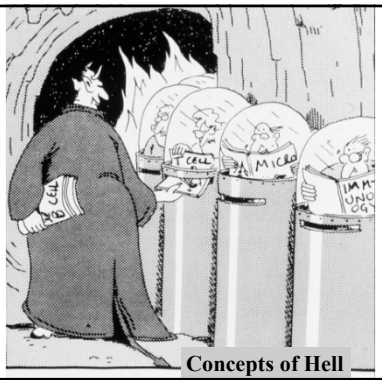
Steven M. Holland, MD
Laboratory of Clinical Immunology and Microbiology
NIAID, NIH

7/22/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**



Concepts of Hell

Host Immune Defense

Humoral
- Complement
- Mannose binding lectin
- Antibody

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

Basic Principles

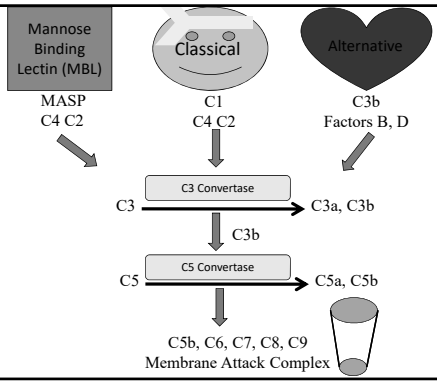
Patients with impaired inflammation:
- may be unable to tell you they are sick (feel fine)
- are often sicker than they look
- often have more extensive disease than is apparent
- may require longer treatment than normals
- may have unusual infections

Who's Got a Problem?

Abnormal frequency of infections
- recurrent *Neisseria* bacteremia
- recurrent pneumonia

Abnormal presentation of infections
- necrotic cutaneous ulcers (not anthrax)
- *Aspergillus* pneumonia

Specific unusual infections
- *Pneumocystis jiroveci*
- *Burkholderia cepacia*
- *Nontuberculous mycobacteria*



Complement Deficiencies

Classical Pathway (C1-C9) (AR)
- Antibody *de*pendent bacterial lysis
- Deficiency leads to recurrent bacteremia and meningitis

Alternative Pathway (Factors I, H, Properdin, C3) (Properdin X-linked, others AR)
- Antibody *in*dependent bacterial lysis
- More severe than classical defects

Mannose Binding Lectin (MBL) Pathway
- Very modest IF ANY defect, mild effect in infancy

Complement Defects

C5-C9 Defects
- recurrent *Neisseria* bacteremia and meningitis
- average age of onset 17 y, milder CNS sequelae
- high rates of relapse and reinfection

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

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

Rx- treat infections, prophylaxis if needed, hypervaccination?

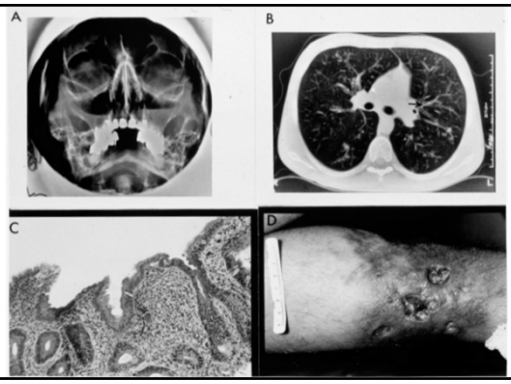
J Clin Immunol 2020 May;40(4):576-591

Antibody Deficiencies

IgA Deficiency (AR)
- common (1/700 adults)
- probably not a pathologic condition *per se*
- frequently associated with other deficits, such as common variable immunodeficiency (CVID), Ig subclass deficiencies

Dx- low IgA

Rx- none



Common Variable Immunodeficiency (CVID)

- recurrent sino-pulmonary bacterial infections
- chronic enteric infections with *G. lamblia, Campylobacter, Salmonella, Shigella*
- severe echoviral meningitis/encephalitis/myositis

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

Rx- treat infections, Ig replacement

47 year old woman

Recurrent episodes of bronchitis, recently more exacerbations. Tired.

One episode of documented bacterial pneumonia and sinusitis.

Immunoglobulin levels:

IgG 500 (normal 523-1482)

IgA <10 (normal 51-375)

IgM 165 (normal 37-200)

Next step?

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

52 year old man

referred from his Family Practitioner.

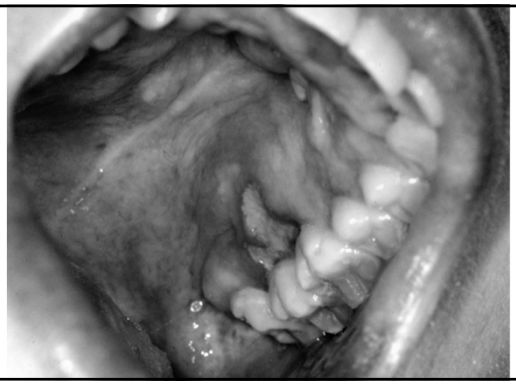
Recurrent digital and oral ulcers occurring every month or so for the last 4 months.

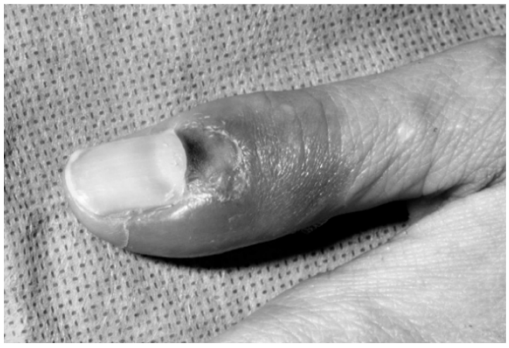
One CBC showed an ANC of 100, but on repeat several days later was normal.

Previous health good.

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

Spleen tip felt.





Cyclic or Acute Neutropenia

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

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

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

Dx- molecular; demonstration of periodicity, family history.

Rx- G-CSF lifts both nadir and baseline

Acquired Neutropenia in Adults

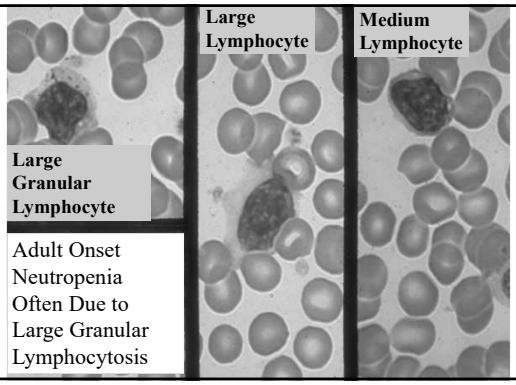
-Drugs, lupus, etc.

-acquired cyclic neutropenia
(Large Granular Lymphocytosis, LGL)
splenomegaly, often associated with rheumatoid arthritis (Felty Syndrome)

Dx- clonal CD3+/8+/57+ lymphs (LGL)
(Gain of Function mutations in STAT3)

Rx- treatment of the abnormal clone is curative (cyclosporine, MTX, steroids)
G-CSF may lift both nadir and baseline

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



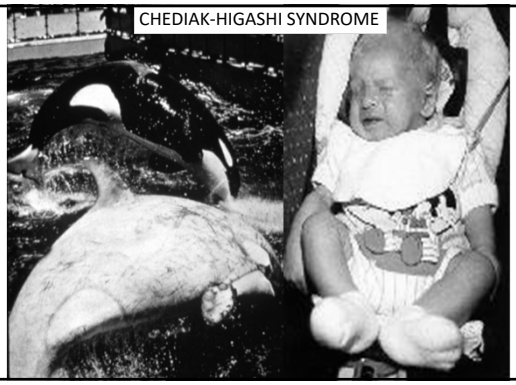
Myeloperoxidase (MPO) deficiency (AR)

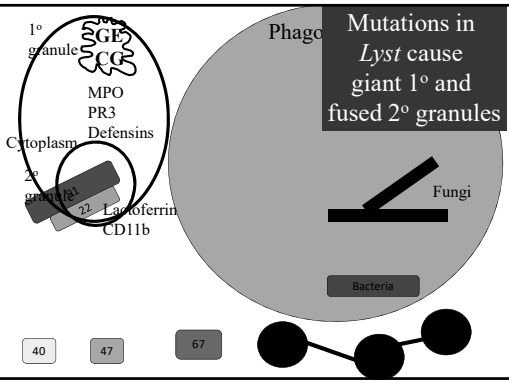
most common neutrophil disorder (1/2000)
- not a pathologic condition *per se*
- failure of H_2O_2 -----MPO-----> HOCl
- compensated by increased H_2O_2 production
- appears to need another condition to potentiate, such as diabetes mellitus

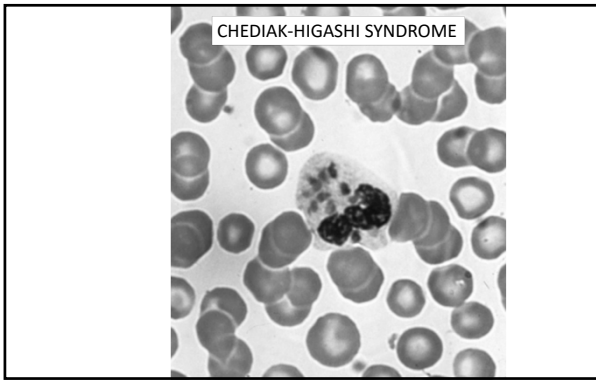
Dx- absence of peroxidase positive granules due to mutations in *MPO* gene

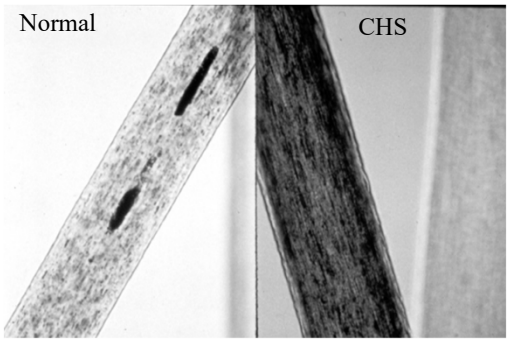
Rx- treat invasive infections (*Candida*), no specific therapy

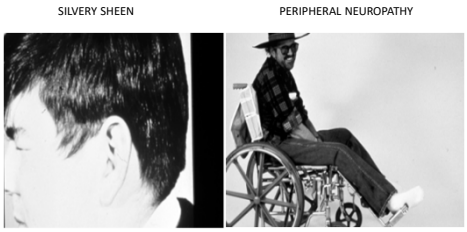
J Leukoc Biol. 2013 Feb;93(2):185-98











Chediak-Higashi Syndrome (AR)

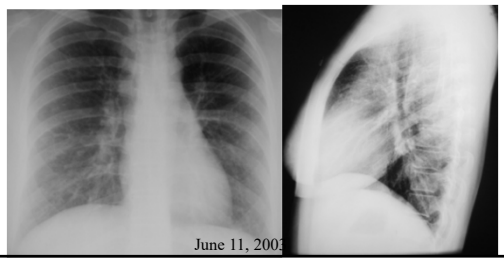
recurrent cutaneous, sino-pulmonary infections
GNR, staph, strep, no fungi
mild neutropenia (intramedullary destruction)
partial oculocutaneous albinism,
mental retardation, neuropathy (late),
lymphoma or HLH-like "accelerated phase" (late)

Dx- giant blue granules; killing and chemotactic defects due to mutations in *CHS1*, encodes LYST
Rx- prophylaxis**,** treatment of infections, BMT

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

23 yo woman; athletic coach

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



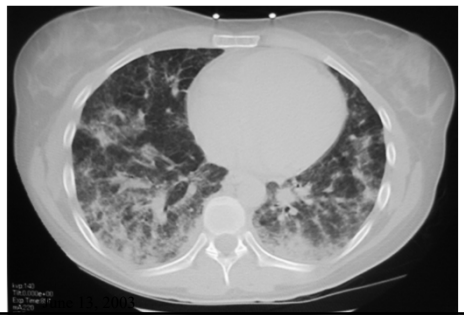
ER presentation

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

PMH
Respiratory infections in infancy
Cat scratch disease 8 yo: resolved with antibiotics

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

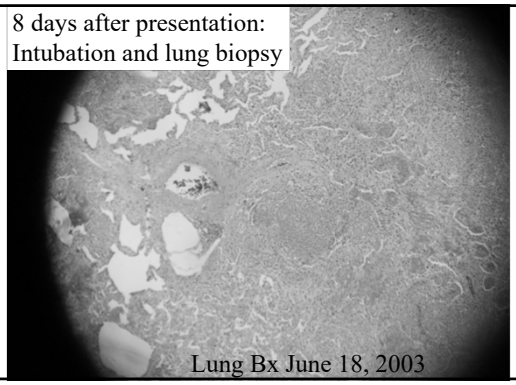
2 days later, hypoxia and fever



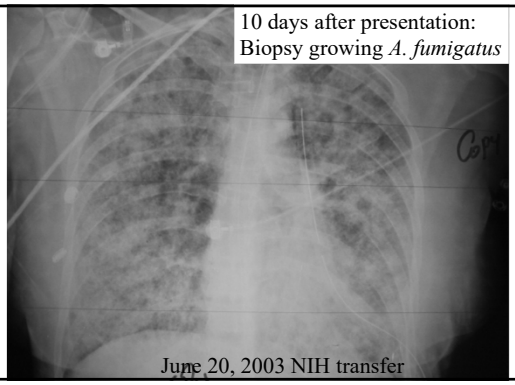
Hospital Course

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

8 days after presentation:
Intubation and lung biopsy



Lung Bx June 18, 2003



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

June 20, 2003 NIH transfer

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

a) Allergic bronchopulmonary aspergillosis
b) Cystic fibrosis
c) Lymphocyte dysfunction (SCID)
d) Phagocyte defect
e) Acute HIV

Chronic Granulomatous Disease
(X, AR)

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

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

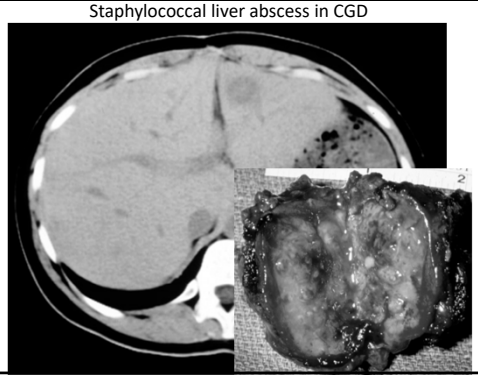
Infections in CGD

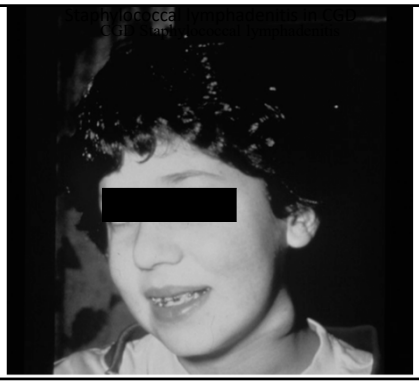
S. aureus	(liver, lymph nodes, osteo)
S. marsescens	(skin, lung, lymph nodes)
B. cepacia	(pneumonia, bacteremia)
Nocardia spp.	(pneumonia, brain, liver)
Aspergillus spp.	(lung, esp. miliary, spine)
Salmonella	(enteric, bacteremia)
BCG	(local/regional infections)

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

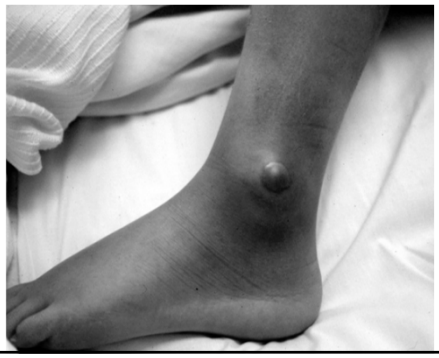
Pediatric Health Med Ther 2020 Jul 22;11:257-268

Staphylococcal liver abscess in CGD

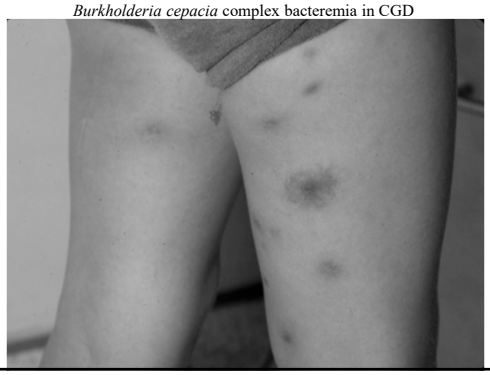




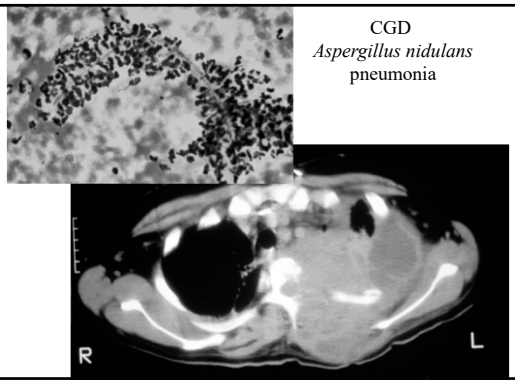
Staph aureus osteomyelitis in CGD



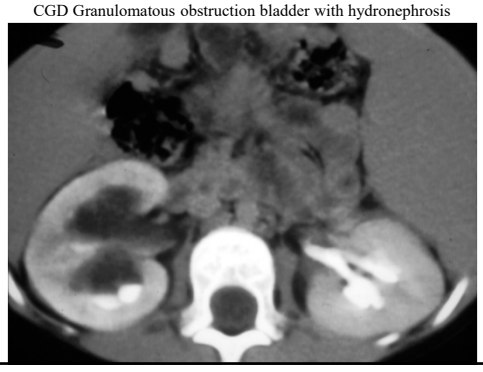
Burkholderia cepacia complex bacteremia in CGD



CGD
Aspergillus nidulans
pneumonia

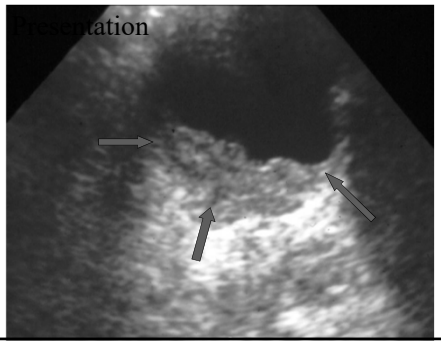


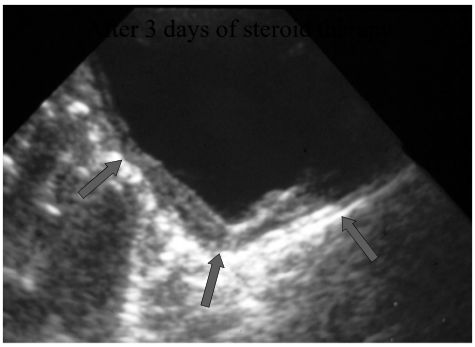
CGD Granulomatous obstruction bladder with hydronephrosis



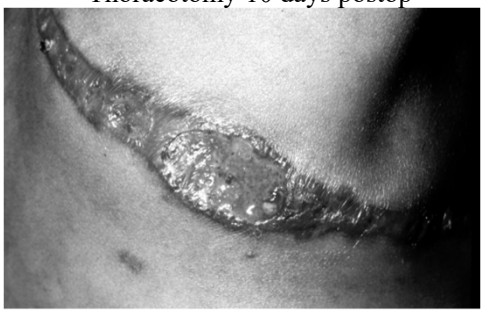
CGD Granulomatous cystitis

Presentation

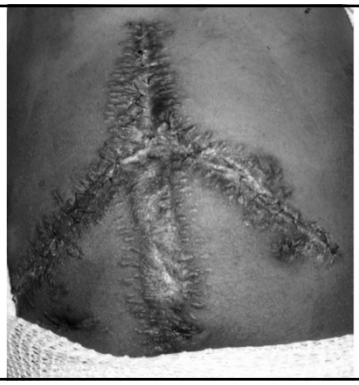




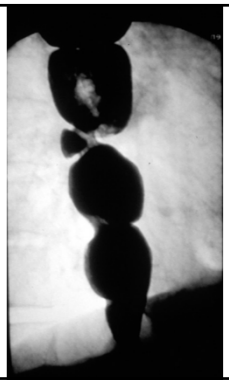
Thoracotomy 10 days postop



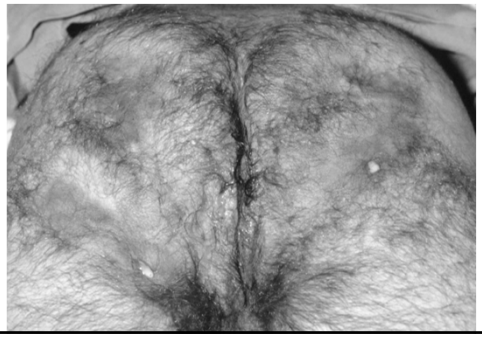
CGD granulomatous wound dehiscence



CGD granulomatous esophageal obstruction



CGD Inflammatory Bowel Disease



Chronic Granulomatous Disease

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

failure to produce superoxide and its metabolites

Dx- PMN dihydrorhodamine 123 oxidation (DHR),
PMN nitroblue tetrazolium reduction (NBT)
(MPO Deficiency gives a FALSE ABNORMAL DHR)
BE CAREFUL ABOUT THE LAB!!!!

CGD Genetics

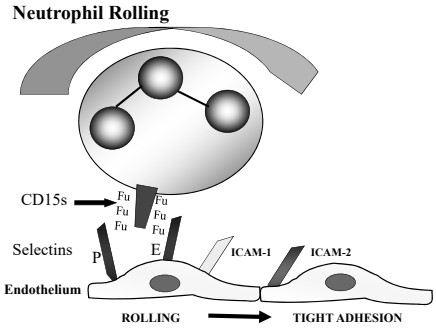
X-linked, chr. Xp21 (70% of cases)
- carrier females are mosaic (Lyonization)
- 1/2 of offspring of carrier Mom will receive the gene
  - about 1/3 of carriers are sporadic, from sperm
- X-linked male: all daughters carriers, no sons affected

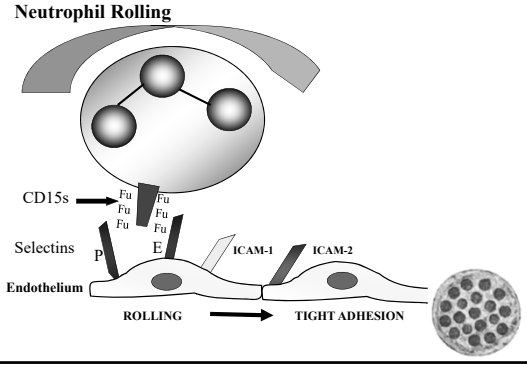
autosomal recessive (30% of cases)
- 1/2000 carry the gene for the most common AR form
  - bad luck happens

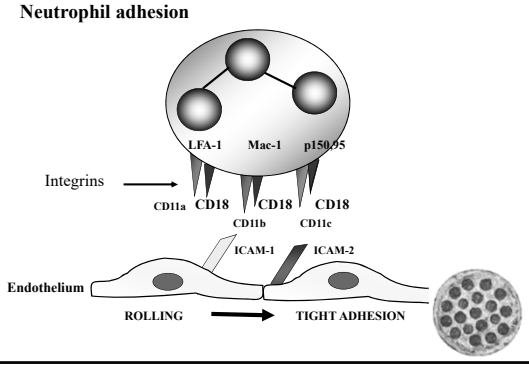
CGD Management and Treatment

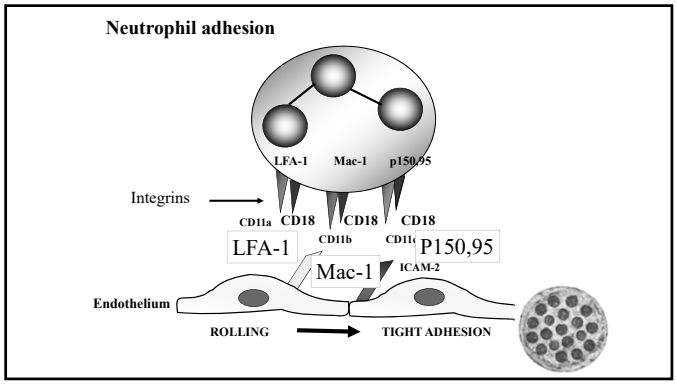
90% overall long-term survival
follow ESR, radiographs
prophylactic antibiotics and antifungals
TMP/SMX, itraconazole
prophylactic interferon gamma
50 µg/m2 subcutaneously three times weekly
aggressive search for and treatment of infections
BMT
(gene therapy)

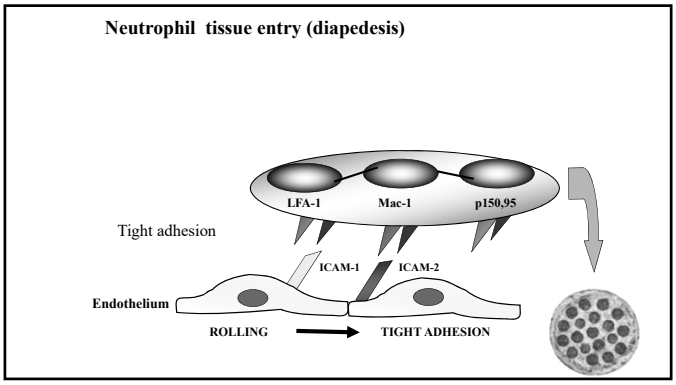
Hematol Oncol Clin North Am. 2013 Feb;27(1):89-99

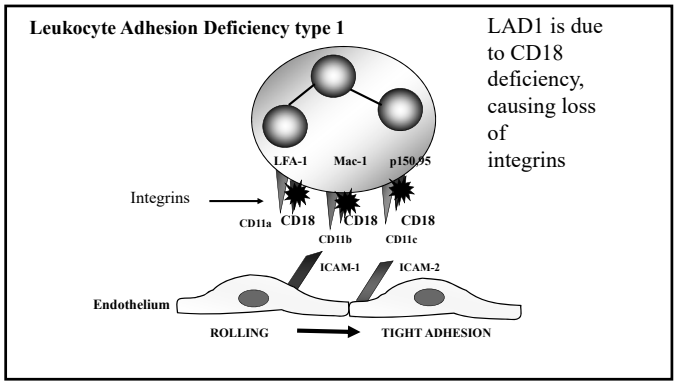












LAD1 is due to CD18 deficiency, causing loss of integrins

Leukocyte Adhesion Deficiency Type 1 (AR)

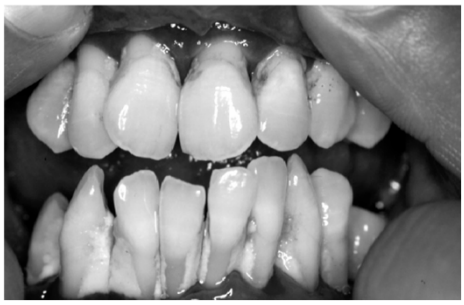
Recurrent necrotizing infections: skin, perineum, lung, gut

Enteric GNR, GPC, NOT fungi or *Candida*

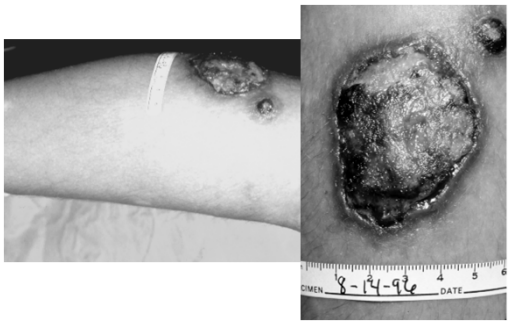
baseline leukocytosis, further WBC increase to infection

rare, consanguinity common

Almost universal tooth loss in LAD1 by adulthood



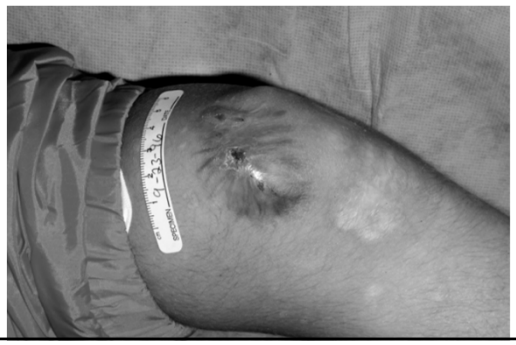
Impaired wound healing in LAD1

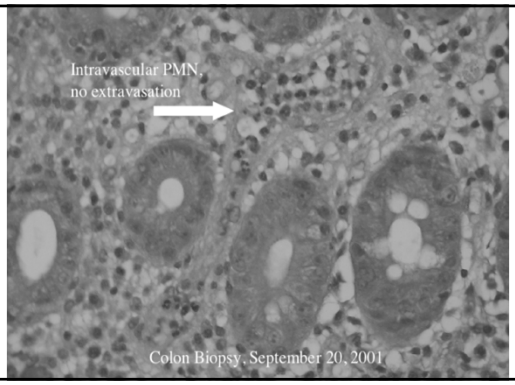


Leukocyte Adhesion Deficiency I

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

Cigarette paper scarring





Leukocyte Adhesion Deficiency 1

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

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

19 year old boy with Pneumonia

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

Ruling against LAD1 would be:

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

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

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

d) Extensive neutrophil infiltration in the left shin ulcer.

e) Multiple dystrophic scars over the legs from previous ulcers

27 year old woman with boils

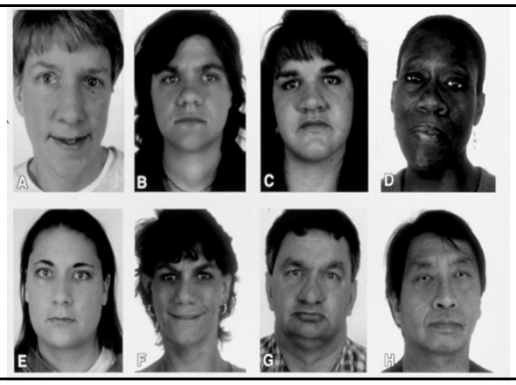
Referred from her internist for recurrent boils with *S. aureus*

IgE of 12,376 IU.

"Bronchitis and sinusitis at least once a year"

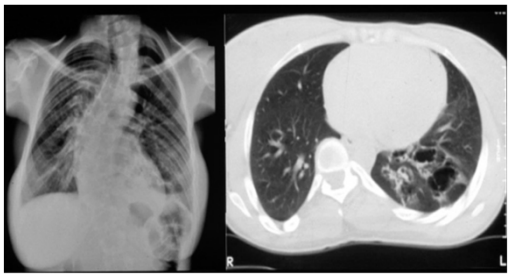
Persistent eczema requiring topical steroids.

Never hospitalized but having "more trouble" lately.



HIE (Job's) Syndrome History and Exam

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



Pulmonary Pathogens in HIE

Primary pathogens:

Staphylococcus aureus

Streptococcus pneumoniae

Hemophilus influenzae

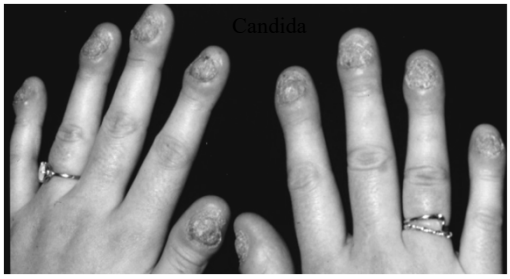
Secondary pathogens:

Pseudomonas aeruginosa

Aspergillus fumigatus

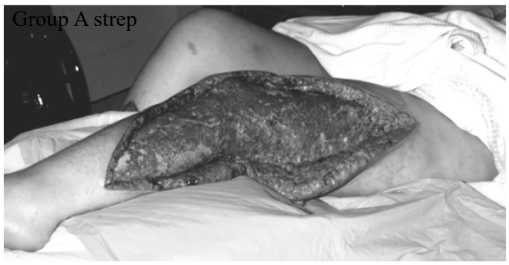
Others:

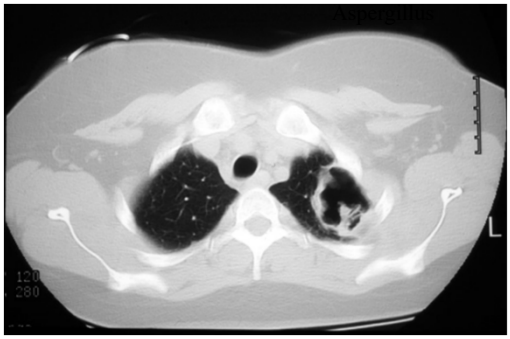
Pneumocystis jiroveci, M. avium complex

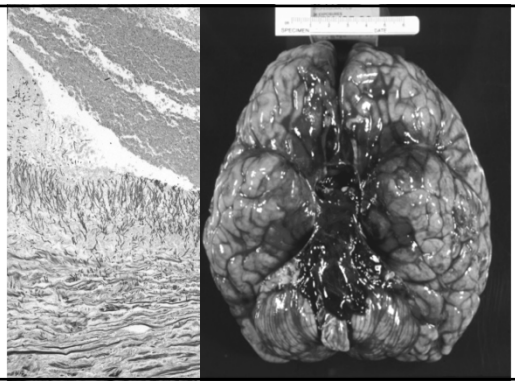


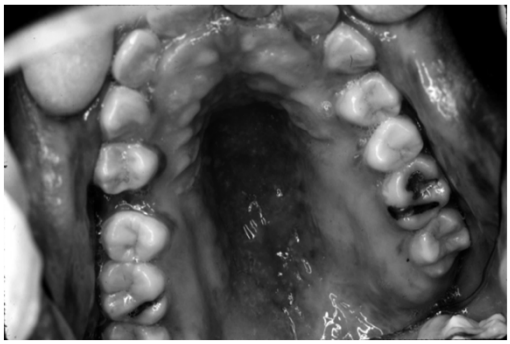
14 - Clinical Immunology and Host Defense

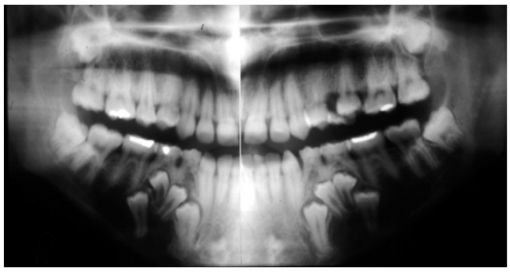
Speaker: Steven Holland, MD







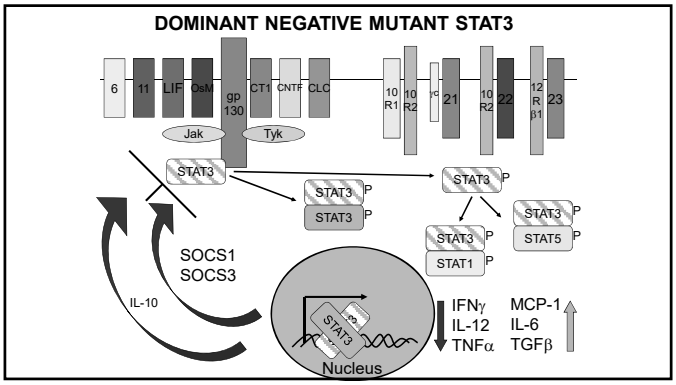




HIE Laboratory Findings

Hyper IgE	97% >2000 IU/ml
Eosinophilia	93% >2SD above mean

No correlation between IgE and eosinophilia
IgE values declined into the normal range in 17%



Hyper IgE Recurrent Infection (Job's)

recurrent sinopulmonary infections *S. aureus, S. pneumo, H. flu*
post-infectious pulmonary cyst formation
recurrent *S. aureus* skin abscesses
characteristic facies, eczema, scoliosis, fractures
very elevated IgE (>2000 IU), eosinophilia

DDx- atopic dermatitis is a close mimic
HIE: onset of rash near birth, pneumonia, lung cysts, skeletal
Mutations in STAT3
Rx- treatment of infections, prophylactic antibiotics, antifungals.
BMT

DOCK8 Deficiency

Autosomal Recessive
Eczema, allergies, asthma, high IgE
Staph, Strep, H. flu, Acinetobacter, Pseudomonas

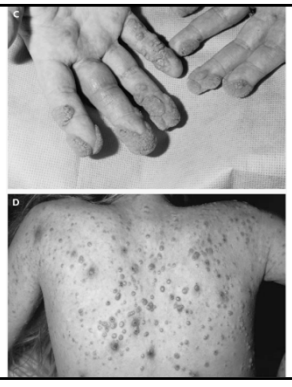
Candida, Cryptococcus, Histoplasma

HPV, HSV, molluscum

Squamous cell carcinomas, lymphoma

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

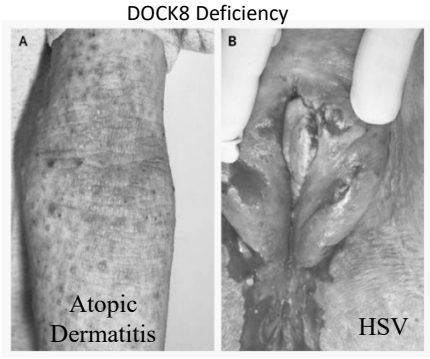
DOCK8 Deficiency



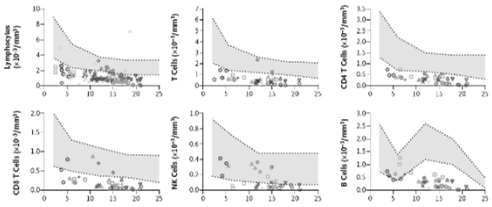
HPV

Molluscum contagiosum

DOCK8 Deficiency



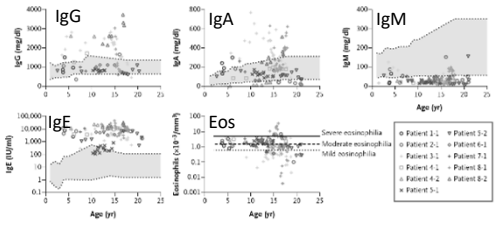
DOCK8: Lymphopenia is common and somewhat progressive



Age in years

NEJM 361:2046, 2009

DOCK8: IgE and eosinophils are high, IgM is low



DOCK8 vs. STAT3 Hyper IgEs

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

15 year old girl with recurrent infections

Infancy: eczema, recurrent pneumonias, skin infections

IgE 14,574 IU/ml

Allergist: use bed covers to avoid dust mites.

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

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

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

18 year old male with lymph node

Referred from hematologist/oncologist

nodes biopsied for Hodgkin showed granulomata and grew *M. avium.*

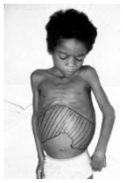
PMH recurrent salmonellosis as a child.

Sibling had tuberculosis but is now cured.

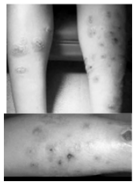
CD4+ number is normal, HIV -

Clinical Spectrum of NTM Infections

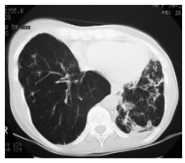
Disseminated
Severe, Young
IFNγ/IL-12 defects
NEMO, STAT1



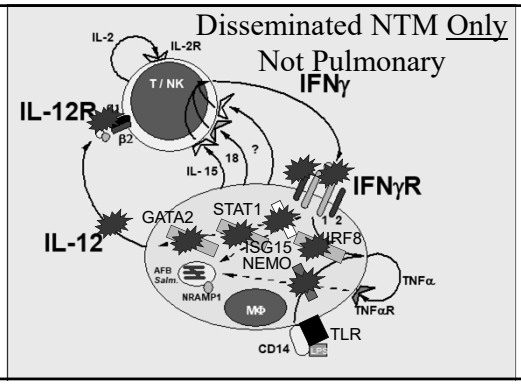
Skin
Exposure
Inoculation

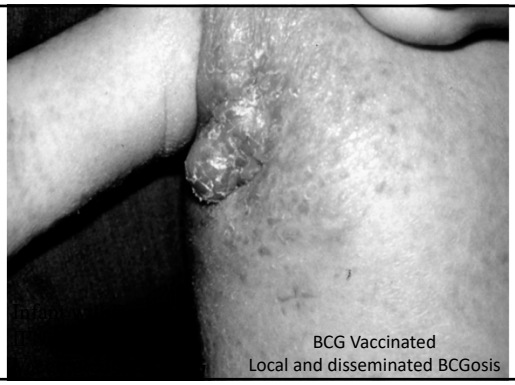


Pulmonary
Chronic, Older
Bronchiectasis
Cystic fibrosis (CF)
Ciliary dyskinesia (PCD)

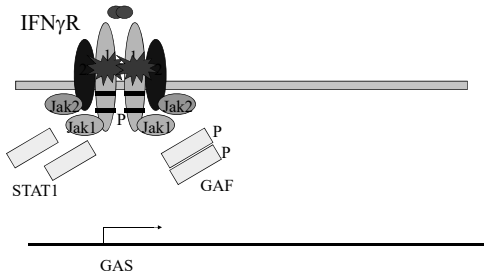


Disseminated NTM Only Not Pulmonary

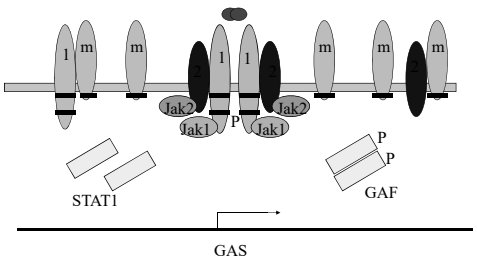




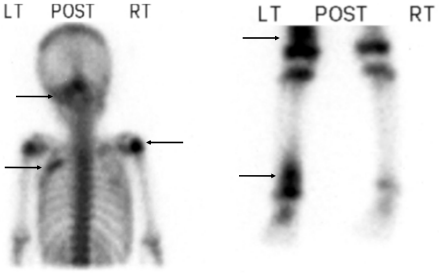
Autosomal Recessive IFNGR1 (both alleles)



Autosomal Dominant IFNGR1 (one allele)



Mycobacterial Osteomyelitis in Dominant IFNγR1 Deficiency



IFNGR1: Dominant vs. Recessive

Characteristic	AD	AR
IFNγR1 display	high	none
IFNγ responsiveness	low	none
Clinical presentation	local	disseminated
Granulomata	present	absent
Osteomyelitis	100%	rare
Survival	excellent	most die

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

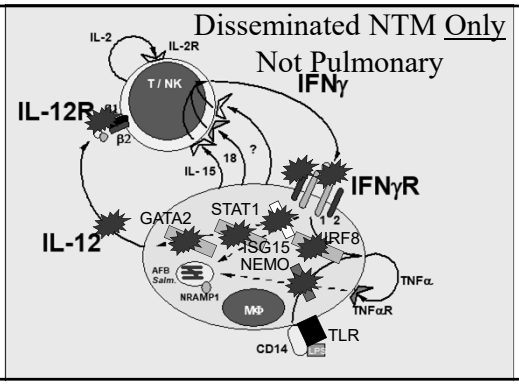
Interferon γ Receptor Deficiencies

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 for recessive)

N Engl J Med. 2017 Sep 14;377(11):1077-1091.

Disseminated NTM Only
Not Pulmonary

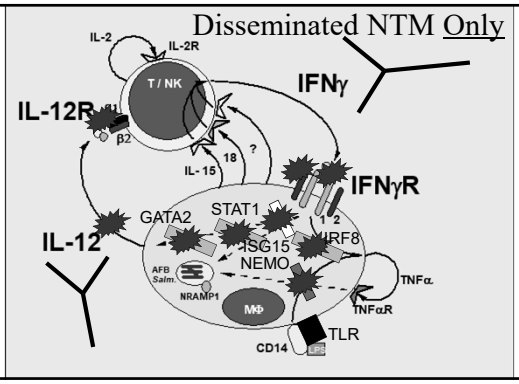


IL-12βR1 Deficiency

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

Dx- genetics, flow cytometry
Rx- antimycobacterials, IFNγ systemically

Disseminated NTM Only



Anti-IFNγ autoantibody syndrome

Disseminated NTM later in life
Predominantly female, mostly East Asian
NTM, TB

Dx- autoantibody detection
Rx- antimycobacterials, possibly rituximab

NEJM 2012;367:725

20 yo with back pain

WBC 12,000/µl, ESR 93 mm/hr, PPD12 mm
2 weeks pain over L2 and a lytic lesion
Biopsy: histiocytic malignancy, chemotherapy started
Father had similar illness, turned out to be MAC

You suspect that she has the autosomal dominant form of IFNγR1 deficiency and you need to prove it before radiation starts.

To confirm the diagnosis, you should:

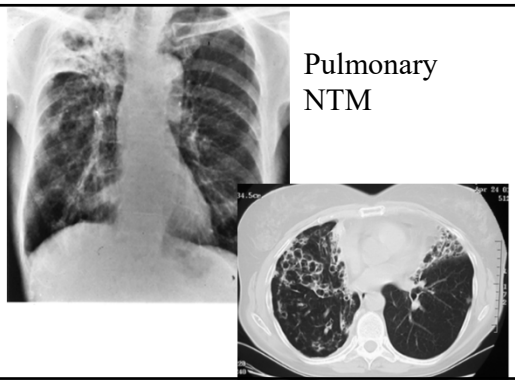
a) Show high TNFα from stimulated cells
b) Show high IL-12 from stimulated cells
c) Show high IFNγR1 on cell surfaces
d) Show high TNFαR on cell surfaces
e) Show low IFNγR1 on cell surfaces

GATA2 Deficiency

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

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

Blood 2014; 123:809-21



Pulmonary NTM

Pulmonary NTM: Adults

Female predominance
Caucasian predominance
Post menopausal
"Lady Windermere Syndrome"
tall, thin, pectus abnormalities
Association with CFTR mutations
Complex immunologic and somatic genetics

Szymanski Am J Respir Crit Care Med. 2015

Remember

Disseminated NTM means immunodeficiency

Corollary: Isolated Pulmonary NTM Does not

CD4+ T-lymphocytopenia

HIV associated

autoimmune associated

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

Dx- determination of ICL (FACS)

Often due to an underlying defect, so LOOK

Rx- treat infections (follow CD4+, ?cytokines)

Screening Laboratories

For Lymphocytes

- Ig levels
- immunization status (tetanus, pneumovax)
- CD4+ number
- Genetics (exome studies, panels)

Screening Laboratories

phagocytes

- DHR for superoxide
- FACS (CD18, CD11a-c, IFNγR1, IL-12Rβ1)

complement

- CH_{50} (classical pathway)
- AH_{50} (alternative pathway)
- ELISA for individual components

Think about the gene involved!

Use Pubmed OMIM

- sequence gives a solid diagnosis

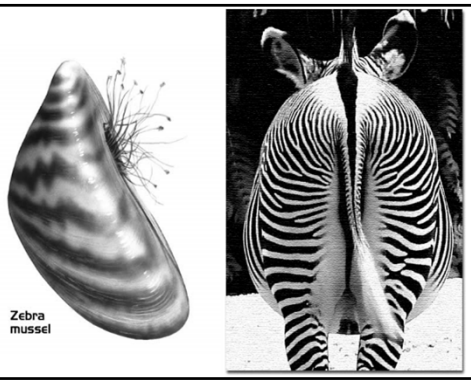
It is the SOS

History

Physical

Imaging

Laboratories
(talk to the lab yourself!!!)



15

Gastrointestinal Disease: Etiologic Agents

Dr. Herbert DuPont

15 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Gastrointestinal Disease: Etiologic Agents

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School
School of Public Health
Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

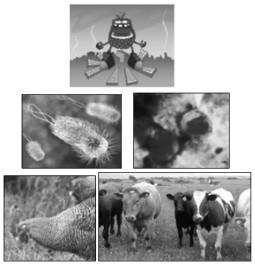
7/7/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

OBJECTIVES



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

ANNUAL DEATHS FROM ENTERIC PATHOGENS IN U.S.

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

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

PATHOGEN COMMUNICABILITY
ALL INFECTIOUS DISEASES SHOW A DOSE THRESHOLD FOR ILLNESS

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

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

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

QUESTION #1

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

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

15 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

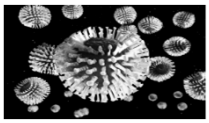
VIRAL GASTROENTERITIS

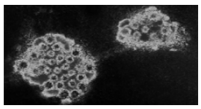
ROTAVIRUS

- KILLER OF 129,000 INFANTS GLOBALLY WITH DECREASES AS VACCINES ARE MADE AVAILABLE
- DECREASED RATES WORLDWIDE THANKS TO INEXPENSIVE VACCINES

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

- 200,000 ANNUAL DEATHS IN THE DEVELOPING WORLD WITH YOUNG CHILDREN AND THE ELDERLY MOST SUSCEPTIBLE
- > 20 MILLION CASES FOODBORNE DISEASE IN U.S. (HALF OF ALL CASES); 26% OF CASES PRESENTING TO ED
- 20% OF U.S. POPULATION NOT SUSCEPTIBLE RELATED TO ANTIGENS THAT DETERMINE BLOOD TYPES
- MAJOR PATHOGEN GENO GROUP II GENOTYPE 4 (GII.4) WITH GII.17 STRAINS CURRENTLY EMERGING
- SECONDARY ATTACK COMMON (17%)
- MOST COMMON SETTING FOR OUTBREAKS HEALTHCARE FACILITIES, AND NURSING HOMES





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

***E. COLI* O157**

SORBITOL-NON-FERMENTING

SORBITOL-MACCONKEY AGAR & O157 SEROTYPING

E. coli* non-O157

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

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

Hemorrhagic colitis

Dysentery

85%

13%

Hemolytic Uremic Syndrome

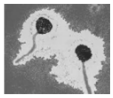
9%

9%

STEC strains are threatening our food supply

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

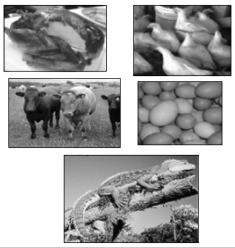
SHIGA TOXIN PRODUCTION UNDER PHAGE CONTROL



- SOME ANTIBIOTICS MOBILIZE PHAGE (E.G. FLOUROQUINOLONES, TMP-SMX),

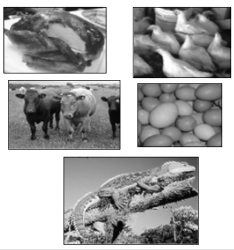
  AZITHROMYCIN AND RIFAXIMIN DO NOT
- ANTIBIOTICS ARE NOT INDICATED IN THIS INFECTION BUT STAY TUNED
- HUS CAN BEGIN AS SYMPTOMS RESOLVE USUALLY WITHIN 3 WEEKS OF INFECTION. ~15% OF CHILDREN DEVELOP, LESS IN ADULTS WITH INCREASING RATE IN ELDERLY. DEATH RATE 3-5%
- WHILE COMPLEMENT IS INVOLVED IN TYPICAL HUS, ANTI-COMPLEMENT MONOCLONAL ANTIBODIES (ECULIZUMAB AND RAVULIZUMAB) ARE APPROVED ONLY FOR ATYPICAL HUS
- TREATMENT IS SUPPORTIVE: DIALYSIS, ACE INHIBITORS, ARBS FOR CONTROL OF HYPERTENSION AND ANTI-SEIZURE DRUGS

NON-TYPHOID SALMONELLOSIS



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

NON-TYPHOID SALMONELLOSIS



- THE HIGHEST FREQUENCY OF INFECTION IS IN INFANTS. INFANTS WITH MILK-FILLED STOMACHS CAN BE INFECTED BY LOW INOCULUM SIZE DURING HOUSEHOLD CROSS-CONTAMINATION
- IN A STUDY OF 8,770 PATIENTS WITH INVASIVE DISEASE (POSITIVE BLOOD OR BONE MARROW CULTURE) MORTALITY RATE VARIED BY REGION: AFRICA 17%, ASIA 14%, EUROPE AND USA 10%[1]
- RECENT OUTBREAKS HAVE BEEN TRACED TO PEANUT BUTTER (*S* SENFTENBERG) AND CHOCOLATE PRODUCED IN BELGIUM (MONOPHASIC AND NONMOTILE STRAIN OF *S* TYPHIMURIUM)

1 Marchello CS et al. Lancet Infect Dis 2022;22:692-705

PROTOZOAL PATHOGENS CAUSE PROTRACTED DIARRHEA

- PERSISTENT DIARRHEA (≥ 14 DAYS)
- DIAGNOSTIC CHALLENGES

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

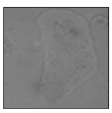
- SPORULATION REQUIRED FOR *CYCLOSPORA* FOR INFECTIVITY
- *CRYPTOSPORIDIUM*

OFTEN HAS AN ANIMALS RESERVOIR, WATER VEHICLE OF TRANSMISSION

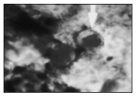
- *E. HISTOLYTICA* PRODUCES LIVER ABSCESS MOST IMPORTANTLY IN MALES

SEROLOGY HELPFUL IN HEPATIC ABSCESS AS STOOLS OFTEN NEGATIVE

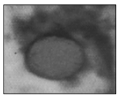
Giardia



E. histolytica



Cryptosporidium



Cyclospora

15 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD

SEAFOOD FOODBORNE DISEASES

Dinoflagellates (DF) in water are the Source of toxin

Neurotoxigenic Illnesses:

- Paralytic Shellfish: toxin from different DF concentrated in in mollusks producing numbness and tingling after 30–60 minutes; serious cases may need respiratory support
- Ciguatera: toxin from DF (*Gambierdiscus toxicus*) growing around coral reefs 35°N and 35°S latitudes, that are ingested by large reef fish ~50,000 each year in world, many in travelers, GI symptoms, cold hot reversal and numbness & paresthesias
- Neurotoxin Inhalation or Shellfish poisoning: toxin from DF *Karenia brevis* inhaled during algal blooms, biggest problem in asthmatics or the toxin is ingested with mild form of paralytic shellfish poisoning
- Pufferfish: toxin from DF in pufferfish (Japanese delicacy)

SEAFOOD FOODBORNE DISEASES

Toxin concentrates in fish or mollusks (histamine-like substances from spoiled fish)

Chemical Illness:

- Scrombroid (histamine-like histidine) from improperly refrigerated or preserved tuna, mackerel, mahi-mahi, sardine, anchovy, herring, bluefish, amberjack and marlin causing a histamine reaction: flushing (like sunburn), headache, palpitations, itching, diarrhea within 10-60 minutes with resolution in 12 hours
- People report a peppery, sharp and salty taste
- Heat stable histamine

WHAT'S NEW TRAVELERS' DIARRHEA

ESBL or MDR Enterobacteriaceae Risk Factors:

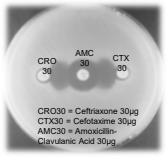
- Travel to tropical and semitropical areas, especially Asia (highest for travel to India)
- Diarrhea increases rate and receipt of antibiotics further increases risk

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

- < 3 months to 12 months
- Shorter than when acquired in a hospital

•Treat with antibiobics only moderate to severe Travelers' diarrhea

Extended spectrum beta lactamase-producing Enterobacteriaceae



Jiang Z-D, DuPont HL

DIAGNOSTIC APPROACHES IN INFECTIOUS DISEASES MOVING TO PCR

Verigene Luminex Biofire

Biocode

Requires clinical judgement & correlation

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

2017 INFECTIOUS DIARRHEA GUIDELINES (HIGHLIGHTS)

- Exercise clinical judgment when interpreting PCR-based results
- Perform reflex cultures when an organism is identified by PCR for epidemiology and susceptibility testing
- Fecal leukocyte, lactoferrin, calprotectin are not routinely indicated
- Diagnostic testing is not indicated for travelers' diarrhea unless diarrhea persists >14 days, consider *C. difficile* if antibiotic exposure. TD can trigger inflammatory bowel disease or irritable bowel syndrome
- Monitor Cr/Hb in patients with STEC identified in stools at risk for HUS, examine peripheral smear for schistocytes
- Perform endoscopy for persistent, unexplained diarrhea

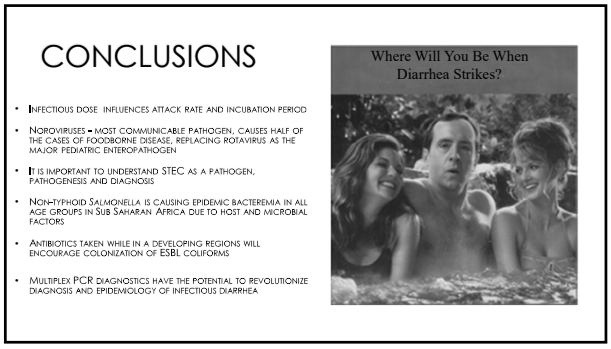
Shane, et. al. CID 2017:65 e45-80

ORGANISM-SPECIFIC THERAPY

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

15 – Gastrointestinal Disease: Etiologic Agents

Speaker: Herbert DuPont, MD



16

Gastrointestinal Disease: Clinical Syndromes

Dr. Herbert DuPont

16 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Gastrointestinal Disease: Clinical Syndromes

Herbert L. DuPont, MD
Professor, Infectious Diseases, Epidemiology
The University of Texas McGovern Medical School
School of Public Health
Clinical Professor, Infectious Diseases
Baylor College of Medicine and MD Anderson Cancer

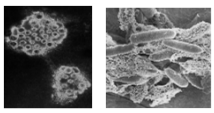
7/7/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

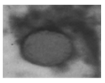
- **None**

OBJECTIVES


Noroviruses

E. coli


Shigella


Cyclospora

- Describe clinical characteristics of various forms of enteric infection syndromes and seafood-associated illnesses
- Outline methods employed in foodborne outbreak investigation
- Define the current status of therapy of dysenteric travelers' diarrhea
- Explain the important post-diarrhea chronic complications
- Explain principles of workup of persistent diarrhea

EVALUATION OF CASES OF DIARRHEA
KEYS CLINICAL FEATURES SPECIAL SETTINGS

VOMITING AS THE PRIMARY SYMPTOM

- Viral gastroenteritis with incubation period: 24 – 48 hours
- Food poisoning Performed toxin* of *Staphylococcus aureus* or *Bacillus cereus* with incubation period: 2-7 hours

**Clostridium perfringens* food Poisoning preformed toxin causes watery diarrhea without vomiting, incubation period of 8-14 hours

INDIVIDUAL CASES KEYS TO ESTABLISH CAUSE

CLINICAL FEATURES
SETTING (EPIDEMIOLOGY)
LABORATORY TESTING

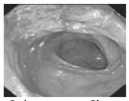
16 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

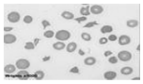
PREVIEW QUESTION

83-YEAR-OLD MAN WITH BLOODY DIARRHEA DEVELOPS RENAL FAILURE

- He has a one week history of diarrhea with stools containing blood; he undergoes colonoscopy which looks like ischemic colitis
- As his diarrhea improves his urine output decreases
- Serum creatinine is 9, platelet count of 50,000, hematocrit 20 and LDH 1,000.
- Stool culture on Sorbitol MacConkey Agar grows only sorbitol-fermenting *E. coli* and stool sample is positive for Shiga toxin 2 by EIA
- He is treated with hemodialysis



Colonoscopy Shows "Ischemic Colitis"



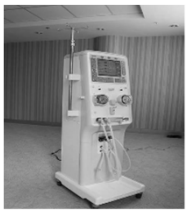
Peripheral Smear Shows Red Cell Fragments

QUESTION #1

PREVIEW QUESTION

What is the likely cause of dysentery and renal failure in the elderly man?

A. Ischemic bowel disease
B. Non-O157 Shigatoxin producing *E. coli* (STEC)
C. O157:H7 strain of STEC
D. *Shigella dysenteriae* 1 (Shiga bacillus)
E. *Campylobacter jejuni*



QUESTION #2

PREVIEW QUESTION

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

What is the likely diagnosis?

A. Scombroid
B. Paralytic shellfish poisoning
C. Ciguatera
D. Neurotoxic shellfish poisoning
E. Monosodium glutamate toxicity

QUESTION 3

- A 65-year old chairman of medicine at a medical school with 15 days of diarrhea, passing 4-8 watery stools per day without fever or passage of bloody stools. He has not traveled and had an initial workup for diarrhea; standard stool culture and an order for parasites that includes a screen for *Giardia*, *Cryptosporidium* and *Entamoeba*.

Which of the following is the best next approach?

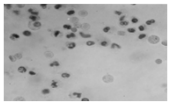
A. Collect 3 stools for parasites by EIA
B. Collect 3 stools for parasites by PCR
C. Perform multiplex PCR for enteric viral, bacterial and parasitic pathogens
D. Ask the laboratory to perform acid-fast staining of stool for parasites
E. Give the patient 1,000 mg azithromycin in single dose

COMPLICATED CASE OF TRAVELERS' DIARRHEA

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

QUESTION 4

Grossly bloody stool



Many leukocytes of stool microscopically indicate diffuse colonic inflammation

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

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

16 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

QUESTION 5

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

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

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

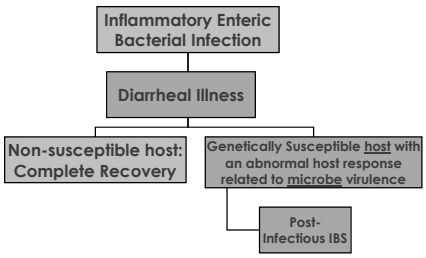
POST-ENTERIC INFECTION DISORDER

THE PATIENT EXPERIENCES A PROTRACTED COURSE

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

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

PATHOGENESIS OF POST-INFECTIOUS IBS



POST-ENTERIC INFECTION DISORDER 2

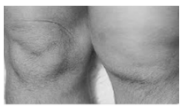
QUESTION 6

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

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

Post-Enteric Infection Disorder 2

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



QUESTION 7

WHAT IS ANOTHER ANTIBODY-MEDIATED POST-ENTERIC INFECTION SYNDROME?

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

16 – Gastrointestinal Disease: Clinical Syndromes

Speaker: Herbert DuPont, MD

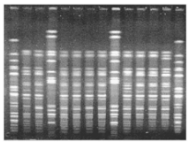
OUTBREAK INVESTIGATIONS

KEYS
EPIDEMIC CURVE
CLINICAL FEATURES
INCUBATION PERIOD
CASE-CONTROL STUDIES OF CAUSE

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

- ON MAY 19, 2009, THE PULSENET NATIONAL MOLECULAR SUBTYPING NETWORK IDENTIFIED A CLUSTER OF 77 CASES OF *E. COLI* INFECTION FROM 30 STATES WITH IDENTICAL PFGE PATTERN
- CASES OCCURRED BETWEEN MARCH 1 AND JULY 31, 2009
- THE MEDIAN AGE WAS 15 YEARS, 71% WERE FEMALES
- 55% WERE HOSPITALIZED, 18% DEVELOPED HUS AND NONE DIED

PulseNet*



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

PFGE being combined with WGS

CASE CONTROL STUDY PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION

- CONTROLS WERE FOUND FROM CORRESPONDING HEALTH DEPARTMENTS WITH NON-STEC ENTERIC INFECTION
- CONVENTIONAL STEC RISK FACTORS* WERE NOT FOUND

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

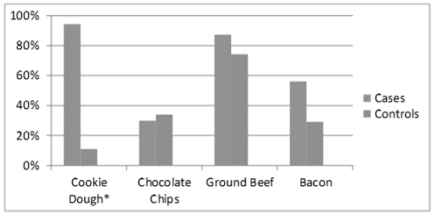
A CASE CONTROL STUDY WAS PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION

- OPENED QUESTIONS IN ONE HEALTH REGION FOUND 5/5 ATE READY-TO-BAKE COOKIE DOUGH

A CASE CONTROL STUDY WAS PERFORMED TO IDENTIFY THE SOURCE

STEP 2: OUTBREAK INVESTIGATION



53% of college student reported eating unbaked homemade cookie dough Byrd-Bredbenner C et al. J Am Diet Assoc 2008;108:549-52

CONCLUSIONS

1. THE CLINICAL FEATURES AND INCUBATION PERIOD PROVIDE CLUES TO THE CAUSE OF ILLNESS
2. KNOW HOW TO DIAGNOSE STEC INFECTION (O157 & NON-O157)
3. MOLECULAR CHARACTERIZATION (PULSENET), THE EPIDEMIC CURVE AND CASE CONTROL STUDY ARE KEYS TO FOODBORNE OUTBREAK INVESTIGATION
4. CONSIDER PI-IBS IN PERSONS WITH PERSISTENT ABDOMINAL PAIN AFTER DIARRHEA BOUTS
5. LEARN SEAFOOD SYNDROMES
6. MULTIPLEX PCR WILL HELP DEFINE THE CAUSES OF DIARRHEA AND IS MOST VALUABLE IN WORKUP OF PERSISTENT DIARRHEA

17

Fungal Diseases in Normal and Abnormal Hosts

Dr. John Bennett

17 – Fungal Disease in Normal and Abnormal Hosts

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Fungal Disease in Normal and Abnormal Hosts

John E. Bennett, MD
Bethesda, Maryland

7/12/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

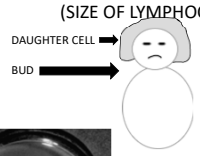
- **None**

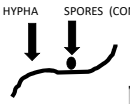
For those not easily offended……
I offer you the basics!!

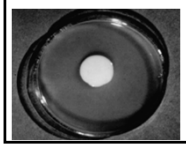
WHAT IS A FUNGUS??

The basics: FUNGI ARE YEASTS OR MOLDS
OR BOTH: YEAST IN THE BODY AND MOLD IN CULTURE (DIMORPHIC)

YEAST (SIZE OF LYMPHOCYTE) MOLD (longer, WIDER THAN BACTERIA)

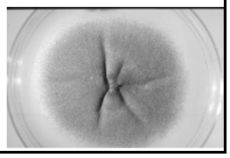






Smooth colony (Cryptococcus)

Fuzzy colony (Aspergillus)



Moving on to the Advanced Course:
Good sources of board exam questions

- Recognize clinical features and host factors for
  - Histoplasmosis
  - Cryptococcosis
  - Coccidioidomycosis
  - Blastomycosis
  - Candidiasis
  - Aspergillosis
  - Mucormycosis
  - Fusariosis
- Know exposures and endemic areas of histoplasmosis, coccidioidomycosis, and maybe paracoccidioidomycosis

Case 1

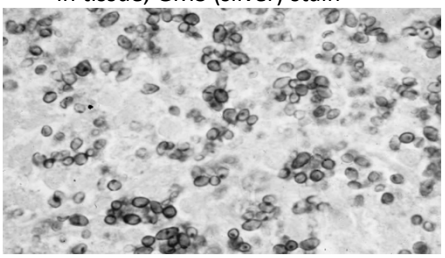
• 42 yr WF with Crohn's disease taking adalimumab is admitted to a Chicago hospital because of 6 weeks of low grade fever, pancytopenia and a 10 pound weight loss. Hydrocortisone 200 mg daily was begun for low serum cortisol not responding to Cortrosyn stimulation. Admission studies found her long standing anemia has worsened, with a hematocrit of 25%, platelet count 30,000, WBC 2,500 with a normal differential, alkaline phosphatase 250, ALT 120, AST 89 and creatinine 2.0 Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture. This infection came from:

a. Her intestinal tract
b. Human (coughing)
c. Pigeon droppings
d. Soil
e. Contaminated food

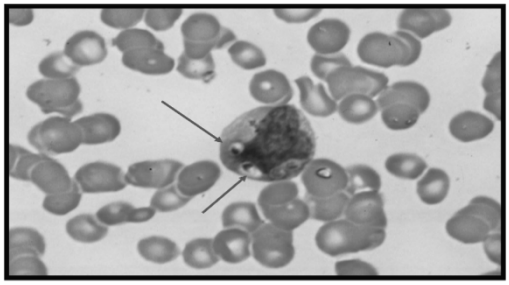
Histoplasma capsulatum

- Central USA highest exposure. Rich moist earth. Subclinical common.
- Disseminated infection mostly immunosuppressed, variable clinical presentation. Fatal in untreated
- Subacute or chronic. Fever. Cytopenias. Addison's. Endocarditis. Mucosal lesions in mouth, larynx, bowel. Miliary lung lesions.
- Diagnosis: antigen in serum, urine or CSF, pathology, culture is slow.
- Rx: ampho if severe. Itraconazole.

HISTOPLASMA CAPSULATUM
in tissue, GMS (silver) stain

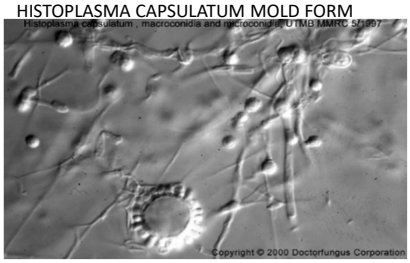


HISTOPLASMA CAPSULATUM YEASTS IN MONOCYTE

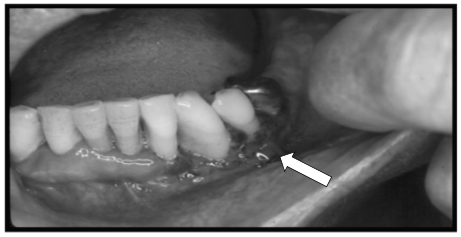


Histoplasma capsulatum growing at room temperature

- HISTOPLASMA CAPSULATUM MOLD FORM

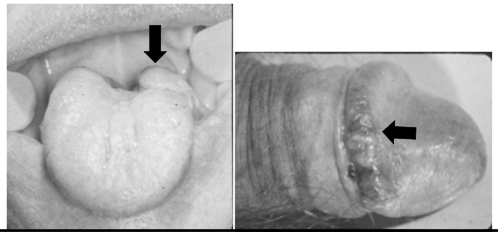


Gingival Ulcer

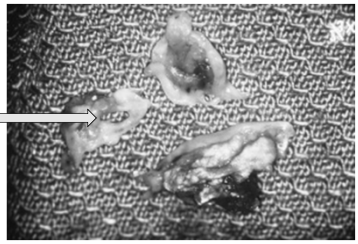


¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

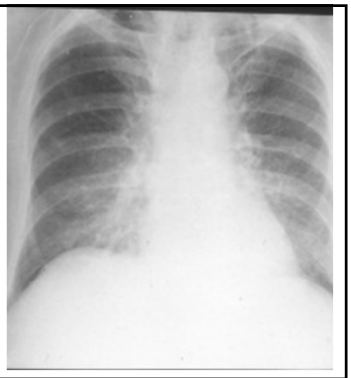
TONGUE AND PENILE LESIONS
MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA



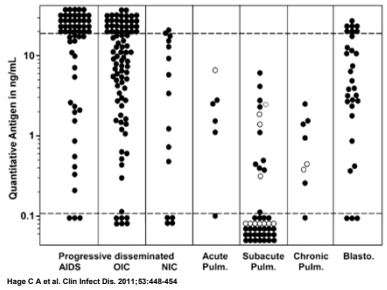
HISTOPLASMA IS A CAUSE OF "CULTURE NEGATIVE" ENDOCARDITIS
(PERFORATED AORTIC VALVE)



MILIARY LUNG LESION IN
DISSSEMINATED HISTOPLASMOSIS
(LOOKS LIKE PCP ON IMAGING)



Results for cases of proven and probable histoplasmosis and proven blastomycosis.



Hage C A et al. Clin Infect Dis. 2011;53:448-454

Clinical Infectious Diseases

REVIEW:
DISSEMINATED HISTOPLASMOSIS
- TNF ALFA INHIBITORS, AIDS, CORTICOSTEROIDS, IMMUNOSUPPRESSION
- NEUTROPENIA DOESN'T PREDISPOSE

SOURCE: INHALATION OF ORGANIC SOIL ENRICHED WITH BIRD DROPPINGS
CLINICAL FEATURES: ONSET SUBACUTRE OR INDOLENT
- PANCYTOPENIA, ORAL LESIONS , MILIARY LUNG LESIONS, ADDISON'S,
- BLOOD CULTURE-NEGATIVE ENDOCARDITIS. HLH-LIKE SYNDROME

DIAGNOSIS
- YEAST IN BLOOD SMEAR OR BIOPSY. GROWS AS MOLD. (DIMORPHIC)
- ROUTINE CULTURES NEGATIVE. FUNGAL CULTURES OFTEN NEGATIVE.
- URINE OR SERUM ANTIGEN BEST (CROSS REACTS WITH BLASTOMYCOSIS)

TREATMENT:
- AMPHOTERICIN FOLLOWED BY ITRACONAZOLE
- FATAL IF UNTREATED

PREVIEW 2022 PREVIEW QUESTION

Case 2

44 yr previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache. Cranial MRI was normal. Lumbar CSF had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512. Liposomal amphotericin B was begun at 5.0 mg/kg IV daily. On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

PREVIEW 2022 PREVIEW QUESTION

Case 2

The most important next step in this patient is which of the following:

A. start flucytosine
B. start fluconazole
C. Start acetazolamide (Diamox)
D. Begin daily lumbar punctures
E. Start dexamethasone

Cryptococcosis

- Encapsulated yeast inhaled from sources in nature. C. neoformans, worldwide, pigeon droppings., C. gattii: S. California, Vancouver Island, overseas , certain trees
- C. neoformans: corticosteroids, AIDS, normal. C. gattii more often normal patient. Similar diseases.
- Symptoms: indolent onset. Usually present in CNS as headache, altered mentation
- Diagnosis: antigen in serum, CSF. Yeasts on biopsy or smear. Fungal culture good.
- Rx: ampho +/- flucytosine then fluconazole. Maintenance in HIV
- Start ARV after 2-10 wks of antifungal Rx in HIV naïve patients.
- Daily lumbar punctures for pts with opening pressure of at least 25cm and symptoms
- Pregnancy: use ampho until delivery (5FC is category C, azoles all teratogenic)

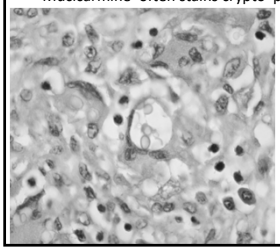
More on Cryptococcosis and IRIS

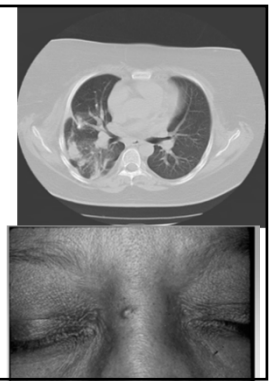
- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDS or prednisone

Cryptococcal lung lesions usually asymptomatic

Skin lesions can resemble molluscum contagiosum

Mucicarmine often stains crypto pink.





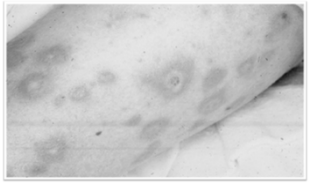
Cryptococcosis review

- Serum antigen good screen in susceptible hosts but can miss early case. LP needed if serum antigen positive. Brain MRI insensitive. CSF antigen sensitive, specific
- Relieve high intracranial pressure to prevent blindness, death
- Start with ampho with fluconazole later. Start with fluconazole if lung only and otherwise healthy
- Wait to start ARV to delay possible IRIS
- Echinocandins not effective

IDBR 2022 PREVIEW QUESTION

Case 3

35 yr male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.



IDBR 2022 PREVIEW QUESTION

Case 3

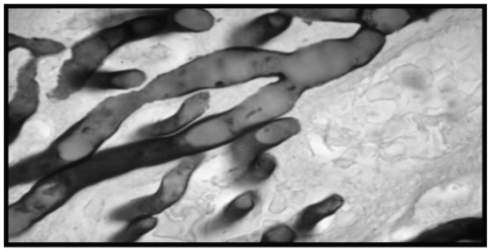
The most likely fungus is which of the following:

A. Scedosporium apiospermum (Pseudallescheria boydii)
B. Lomentospora (Scedosporium) prolificans
C. Apophysomyces elegans
D. Fusarium multiforme
E. Alternaria alternata

Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender skin nodules
Blood culture grows mold in a third to half the patients
RX: response poor in severe neutropenia
PMN transfusions?
Fusarium solani: ampho?
Other Fusarium species : Voriconazole?

Fusarium hyphae. GMS stain



Case 4

- 47 WM executive referred from Baltimore because of severe headaches, diplopia, high fever of 1 wk's duration
- 4 wks PTA: Maui resort one week
- 3 wks PTA: ranch outside Tucson, Arizona 1 wk
- 2 wks PTA: back at work in Baltimore
- 1 wk: PTA: Headache began

- Exam: Temp 38.5 C. Looks ill. Photophobia, nuchal rigidity, right CN6 palsy

- CBC, Routine blood chemistries normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and serum RPR. MRI with contrast normal. Worsens during 2 wks of ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

CASE 4

The most helpful diagnostic test would be:

A. CSF cytology
B. Stool O&P
C. Dietary history
D. Fungal serology
E. Leptospirosis serology

Coccidioidomycosis=Valley Fever

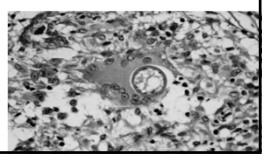
- Two species, one disease:
  - C. immitis and C. posadasii. Both serious lab hazards
  Southwest USA. Washington state
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: African americans, HIV, SOT, TNF inhibitors
- Bone, skin, chronic meningitis
- Rx: fluconazole. Nonmeningeal: itraconazole

COCCIDIOIDOMYCOSIS DIAGNOSIS

SEROLOGY
CSF CF serology useful. Serum CF >16 suggests dissemination, falls with Rx
Serum IgG by EIA converts to positive late, stays positive .
Serum antigen may be useful?

CULTURE
Routine cultures negative, fungal cultures positive. Lab hazard

BIOPSY
Distinctive non-budding spherules



Coccidioidomycosis review

Southwest USA, Washington state

Acute pneumonia 2 weeks after desert dust exposure

Eosinophilia in blood, CSF (low grade)

Dissemination in African Americans, SOT, HIV, pregnancy

CF antibody in CSF, serum

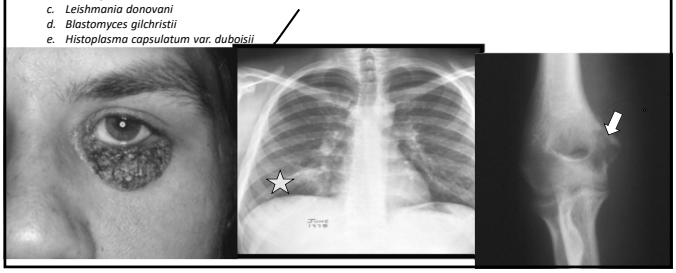
Ampho, itra, fluconazole

CASE 5

A previously healthy 22 yr old Wisconsin man presented with a face lesion, elbow swelling and pain, had asymptomatic lung lesion on chest xray and lytic lesion on condyle of his humerus.

This is most likely which of the following:

a. Candida auris
b. Trichosporon cutaneum
c. Leishmania donovani
d. Blastomyces gilchristii
e. Histoplasma capsulatum var. duboisii



Blastomyces dermatitidis , B. gilchristii

CENTRAL USA AND CANADA, MOLD IN NATURE
LARGE BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

NORMAL HOST

YEAST WITH BROAD BASED BUD, THICK WALL

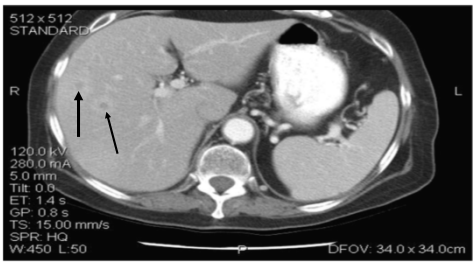
ACUTE PNEUMONIA MAY SELF HEAL

INDOLENT, PROGRESSIVE PNEUMONIA
DISSEMINATES TO SKIN, BONE, MALE GU TRACT

OFTEN PRESENTS AS SKIN LESIONS

RX: ITRACONAZOLE, AMPHO B

Case 6: What are these lesions in a febrile, recently neutropenic patient?



CASE 6

Which is the most likely

A. Babesia microti
B. Candida tropicalis
C. Fusarium oxysporum
D. Aspergillus flavus
E. Streptococcus anginosus

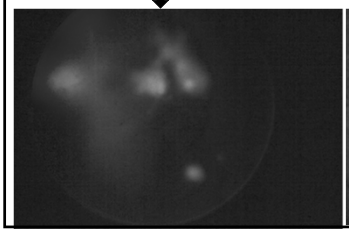
CANDIDA SPECIES

Pseudohyphae and budding yeast
Infected devices usually require removal: catheters, prostheses, grafts
Candidemia may lead to
- hepatosplenic lesions (neutropenics)
- endophthalmitis
- multiple skin lesions (neutropenics)
- endocarditis

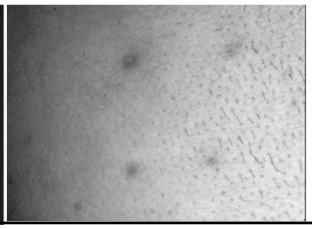
Candida auris often misidentified as unusual species (e g. C. haemulonii,)
Colonizes skin and hospital equipment, causes hospital outbreaks. Contact isolation.
Antifungal drug resistant. CDC: 1012 cases in USA 2021
Echinocandins first choice for all Candida species, including C. parapsilosis, C. auris

Candida endophthalmitis:

"fluff balls" floating in the vitreous humor



Candida lesions in a neutropenic patient

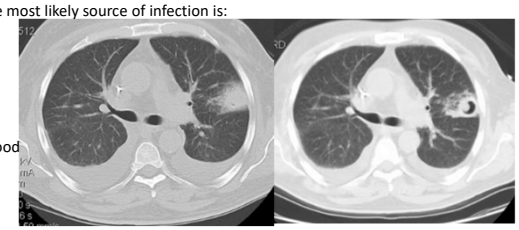


Candidiasis: key points

- Fundoscopy for retinal lesions in candidemia patients.
  - Intravitreal Rx may be needed
- Remove intravenous catheter with candidemia
- Candida auris hospital outbreaks. Poor hygiene
- Fluconazole resistance in C. auris, C. krusei, C. glabrata
- Fungitell (1-3) beta-D-glucan positive in serum

Case 7
32 yr old male with allogeneic hematopoietic stem cell transplant recipient for AML, developed graft versus host disease , given high dose prednisone, discharged and re-admitted for fever not responding to antibacterial antibiotics. These two chest CT 's, were taken at admission and a week later while he was responding to voriconazole. The most likely source of infection is:

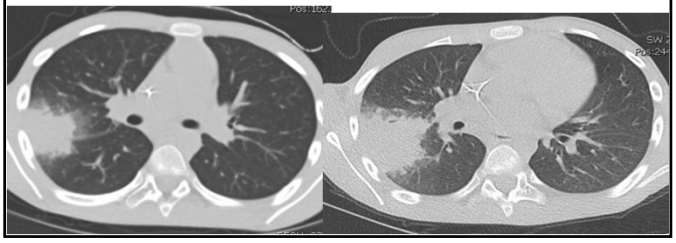
a. Dirt from his garden
b. His oral flora
c. Contaminated food
d. Intravenous catheter



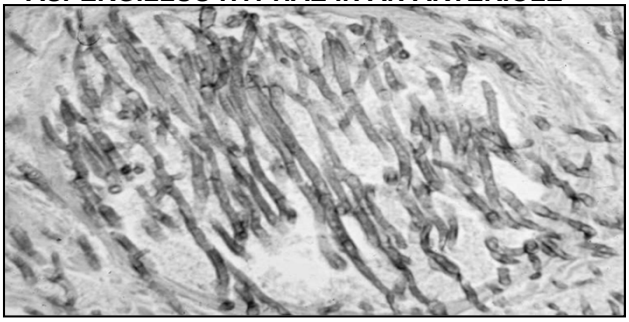
Aspergillus Pneumonia

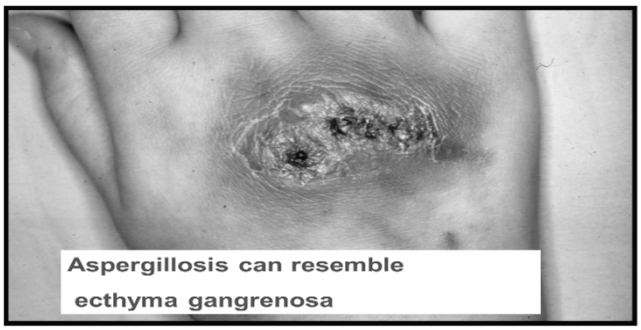
Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis but mucormycosis gives same CT findings: halo sign early, crescent sign later
Septated hyphae invade blood vessels, infarct tissue.
Galactomannan useful in CSF, BAL, blood
False positives
False negatives with azole prophylaxis
Rx. voriconazole, isavuconazole, posaconazole, ampho B

Two CT's showing transient worsening of CT despite clinical improvement . Note halo sign.



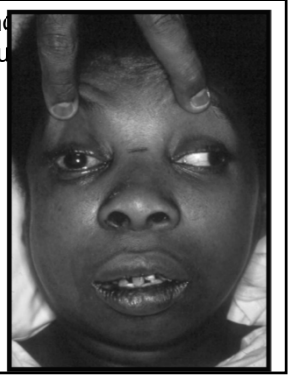
ASPERGILLUS HYPHAE IN AN ARTERIOLE





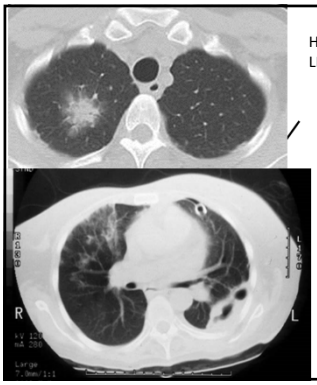
Mucormycosis mimics cavern
following sinu

CASE 8
25 YR OLD FEMALE ADMITTED WITH DIABETIC KETOACIDOSIS AND BLINDNESS IN HER RIGHT EYE. ON EXAM THE RIGHT EYE WAS FIXED IN POSITION AND PROPTOTIC. CT SHOWED DENSE MASS IN ADJACENT ETHMOID SINUS WITH EXTENSION INTO THE ORBIT. SURGICAL EXPLORATION OF THE SINUS SHOWED BROAD, ASEPTATE HYPHAE. THE FUNGUS WAS LIKELY:
A. RHIZOPUS
B. FUSARIUM
C. ASPERGILLUS
D. SCEDOSPORIUM
E. CANDIDA



MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible nonseptate hyphae, right angle branching
- Poorly controlled diabetes melitus, Prolonged neutropenia, corticosteroids
- Massive soft tissue trauma. IV drug abuse
- Hyphae invade blood vessels, causes infarction and necrosis. May form cavity if PMN's return.
- Negative beta d glucan, negative galactomannan
- Rx. Ampho B. Posaconazole f/u. Isavuconazole. Surgical debridement
  Control diabetes

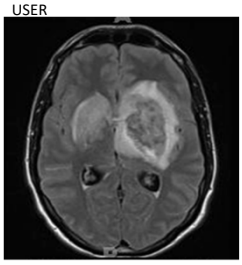


HALO SIGN IN A LEUKEMIC

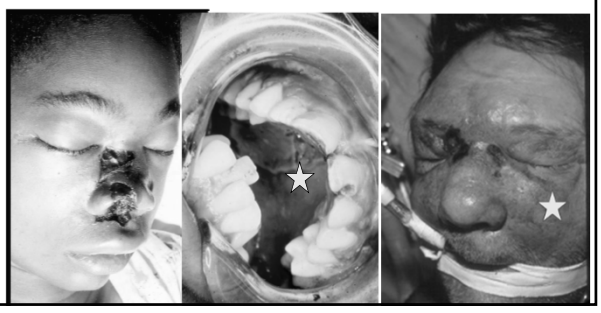
CAVITY AFTER PMN RETURN

MUCORMYCOSIS

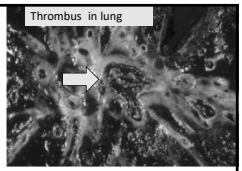
BRAIN ABSCESS IN A HEROIN USER

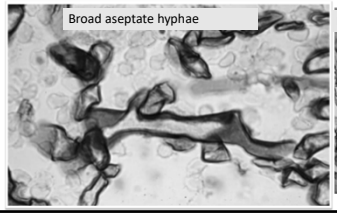


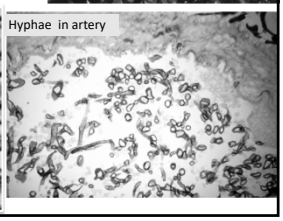
MUCORMYCOSIS
LOCAL EXTENSION FROM PARANASAL SINUS



Mucormycosis: Vascular invasion







MYCOSES WORTH MENTIONING

- SCEDOSPORIUM APIOSPERMUM: IMMUNOSUPPRESSED HOST CLINIALLY RESEMBLING ASPERGILLOSIS . BRAIN ABSCESS AFTER NEAR DROWNING IN POLLUTED WATER. AMPHOTERICIN B RESISTANT
- TRICHOSPORONOSIS: LIKE CANDIDIASIS BUT ECHINOCANDIN RESISTANT
- PARACOCCIDIOIDOMYCOSIS: RURAL CENTRAL AND SOUTH AMERICA. MAY APPEARS DECADES AFTER LEAVING ENDEMIC AREA.
- TALAROMYCOSIS (FORMERLY PENICILLIUM MARNEFFEI). SOUTHEAST ASIA, AIDS, DISSEMINATED INFECTION WITH SKIN LESIONS. YEAST IN BIOPSY, MOLD IN CULTURE.

BR2

Board Review Session 2

Drs. Bennett (Moderator), Aronoff, Chambers, DuPont, Klompas, and Masur

BR2 – Board Review: Day 2

Moderator: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Board Review: Day 2

Moderator: John Bennett, MD
Faculty: Drs. Aronoff, Chambers, Dupont, Klompas, and Masur

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#16 **A 24-year-old healthy woman presents for evaluation of new-onset diarrhea.**

She was in her usual state of health until 2 days ago when she developed abdominal cramps and non-bloody diarrhea. She has no fever or rash, and no one else in the household is ill.

There is no recent travel, though the family visited a nature conservancy a few days ago including a petting zoo with small mammals and reptiles.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#16 **She is HIV negative.**

No therapy is initiated based on your initial consultation but Stool testing was performed.

One day after your initial consultation, the patient's clinical syndrome is unchanged, but the culture yields Salmonella enterica serotype typhimurium.

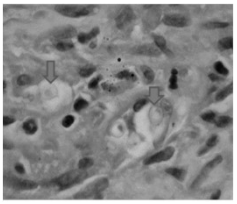
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#16 **How should this patient be managed?**

A) Ciprofloxacin
B) Azithromycin
C) Supportive care (no antibiotics)
D) Amoxicillin
E) Rifaximin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#17 **This lung biopsy shows cells that stain pinkish-red with Mayer's mucicarmine stain.**



INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#17 **The most likely organism is:**

A) *Blastomyces dermatitidis*
B) *Histoplasma capsulatum*
C) *Paracoccidioides brasiliensis*
D) *Cryptococcus neoformans/gattii*
E) *Histoplasma duboisii*

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#18 **A 42-year-old man from New York City developed fever, dyspnea, and increasing pulmonary infiltrates four weeks post-cadaveric single lung transplant. He had been receiving standard 3 drug immunosuppression, but has also required high dose steroids for acute organ rejection.**

He received standard anti-infective prophylaxis.
On bronchoscopy, diffuse alveolar hemorrhage was noted from both lungs.

Biopsy of the transplanted lung showed no evidence of rejection. BAL stains for bacteria, fungi and mycobacteria were negative.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#18 **Biopsy of the transplanted lung showed no evidence of rejection. BAL stains for bacteria, fungi and mycobacteria were negative.**

PCR of blood for CMV was negative.

The transplant center was notified that the recipient of the other lung had developed a similar syndrome. The donor was a 20-year-old recent immigrant from Guatemala who died of a gunshot wound. His mother thought he had been healthy.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#18 **Assuming this infection was acquired from the transplanted lung, which organism appears most likely:**

A) Balamuthia mandrillaris
B) Rabies
C) Cryptococcus neoformans
D) Nocardia brasiliensis
E) Strongyloides stercoralis

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#19 **A 65-year-old male has inflammatory bowel disease treated with infliximab and azathioprine. He has a tunneled subclavian catheter that is used for total parenteral nutrition 5 days per week.**

He has had other medical issues including calcific aortic stenosis: 5 years ago he had a prosthetic aortic valve inserted and is chronically anticoagulated.

He is admitted after 12 hours of fever and shaking chills. He reports no localizing symptoms.

His physical examination is remarkable for temperature of 38.5C, pulse 110 bpm and respiratory rate of 22/min.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#19 **There are no other findings other than a systolic murmur consistent with his prosthetic valve.**

The tunneled subclavian catheter exit site and tunneled area were non-tender and look unremarkable on physical examination.

His CBC shows stable counts with a Hg 10g/dl, WBC 8000/mm^3 and platelet count of 140,000/mm^3.

Chemistry profile is unremarkable.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#19 **Two blood cultures are drawn and he is started on vancomycin, cefepime, and fluconazole.**

The laboratory reports the next morning that the 2 blood cultures drawn through the line are positive for *Staphylococcus aureus* which is determined to be MRSA.

A transthoracic echo (TTE) shows no vegetations or other valve abnormalities.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#19 What management would you recommend?

A) Remove the catheter and treat with vancomycin for 14 days

B) Remove the catheter and treat with vancomycin and gentamicin for 14 days

C) Retain the catheter, continue vancomycin, and obtain a transesophageal echocardiogram before determining therapeutic regimen and duration

D) Retain the catheter and treat with 4-6 weeks of IV vancomycin plus vancomycin lock solution

E) Retain the catheter and treat with 4-6 weeks of IV vancomycin and rifampin plus vancomycin lock solution

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#20 A 38-year-old man has known pulmonary alveolar proteinosis. He is admitted with pneumonia. His treatment has consisted of oxygen and whole lung lavage.

He was in his usual state of health until five days earlier when he had worsening of his usual cough and shortness of breath accompanied by fever, and purulent sputum.

He was given azithromycin as an outpatient but failed to improve. A chest x-ray shows his usual "bat wing" infiltrates and a new consolidated area in the right mid lung.

A sputum Gram stain shows numerous white blood cells and thin (about one-tenth the white blood cell diameter), branching, gram-positive organisms.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#20 Which one of the following is the most likely cause of his pneumonia?

A) Aspergillus

B) Actinomyces

C) Mycobacterium

D) Nocardia

E) Candida

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#21 The surgical intensive care unit and the associated stepdown floor in which you work is struggling with an ongoing cluster of Candida auris infections.

Seven cases have been identified thus far.

The infection control team cohorts all the Candida auris patients into one section of the ICU, places known carriers on Contact Precautions, institutes weekly screening of all uninfected ICU and stepdown patients in order to detect and isolate newly colonized patients early, and institutes daily chlorhexidine baths for all patents.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#21 Hand hygiene is closely monitored and encouraged.

Each patient bay is equipped with a dedicated stethoscope, blood pressure cuff, pulse oximeter, EKG leads, and glucometer.

The only equipment taken from patient to patient are axillary temperature probes that are fastidiously cleaned between each patient.

Despite these measures additional cases are detected.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#21 Best next steps to abort the cluster include:

A) Cleaning each room twice daily with a quaternary ammonium compound

B) Administering prophylactic fluconazole to all patients

C) Switching to disposable temperature probes

D) Changing the curtains between patients' beds daily

E) Flushing all sink drains in patient rooms with bleach foam twice a week

BR2 – Board Review: Day 2

Moderator: John Bennett, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#22 **Which of the following causes of acute diarrhea is least likely to cause post-infectious irritable bowel syndrome?**

A) Shigella spp.

B) Campylobacter spp.

C) Salmonella spp.

D) Clostridium perfringens

E) Yersinia spp.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#23 **An injection drug user is admitted with fever for four days.**

Exam shows a grade IV aortic insufficiency murmur, and he is started on vancomycin 1gm q12h after three blood cultures are obtained.

Methicillin-resistant S. aureus is grown from all admission blood cultures, and repeat blood cultures on days two and three also grow MRSA.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#23 **The vancomycin MIC by E-test for the MRSA isolate is 1.5 mcg/ml.**

On day four of treatment he is short of breath, he has diffuse crackles on chest exam, and x-ray of the chest shows acute pulmonary edema.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#23 **Which one of the following is the most important next step in management of this patient?**

A) Immediate aortic valve replacement

B) Valve replacement once blood cultures are negative

C) Change vancomycin to daptomycin

D) Check a vancomycin level

E) Add rifampin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#24 **A 26-year-old HIV negative woman pregnant for the second time (no prior illnesses) is referred to you by her obstetrician.**

She is 20 weeks pregnant. She has no significant past medical history and reports being in good health prior to this pregnancy.

A screening toxoplasma titer was drawn at the time of her first prenatal visit (week 6) at which time this IFA (IgG) was 1:160. During her first pregnancy, it was 1:80.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#24 **She has been well for the past 20 weeks, and has a normal physical exam for this stage of pregnancy, except for several 1 cm anterior and posterior cervical nodes that she thinks are new.**

On reassessing her history, she does recall several days of malaise, after which she insisted that her husband take care of all cat-related activities at home.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

What advice would you give?

#24

A) She cannot transmit toxoplasmosis to her fetus, thus no further evaluation for toxoplasmosis is needed.

B) A lymph node biopsy should be done to determine if she has acquired toxoplasmosis during this pregnancy, and to then set a course of action.

C) She should have amniocentesis to determine if the fetus is infected, so that a therapeutic plan can be developed.

D) She should be treated with clindamycin and pyrimethamine.

E) Serum IgM, IgG, and IgE anti-Toxoplasma antibody should be sent immediately to a reference laboratory so that a management course can be developed.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

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

There is a family history of gastric cancer.

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

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#25 What would be best option to evaluate this patient regarding Helicobacter infection/disease after completing antibiotic therapy?

A) No further testing is necessary for one year

B) Perform the stool Helicobacter pylori antigen test 8 weeks after treatment

C) Perform the urea breath test 3 weeks after treatment

D) Repeat endoscopy, biopsy and rapid urease test (RUT) 6 weeks after treatment

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#26 A 50-year-old Hispanic woman underwent heart transplant for nonischemic cardiomyopathy.

A month later she has multiple nodules in several organs involved, including brain, and lung.

Skin biopsy culture grew ***Exophiala attenuata***, susceptible to all antifungal agents tested.

She was initially treated with Ambisome and was recently converted to voriconazole.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#26 She calls to report that she developed photophobia and the sensation of lights flashing.

She comes to your clinic: Ophthalmologic examination by an ophthalmology consult is unrevealing.

She has no other new symptoms or findings

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#26 What is the most likely cause of her visual symptoms?

A) Fungal chorioretinitis

B) CMV retinitis

C) Elevated Fluoride level

D) Voriconazole

E) Hypercortisolemia

BR2 – Board Review: Day 2

Moderator: John Bennett, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#27 A 65-year-old patient has been receiving intermittent chemotherapy for esophageal carcinoma through a tunneled subclavian catheter for 6 months.

A week after the most recent infusion, the patient reports 12 hours of a low-grade fever and tenderness over the tunneled catheter.

On examination, the patient is febrile to 38.5C but otherwise has normal vital signs.

The only abnormal physical finding is erythema and tenderness over the tunneled catheter. The exit site has no purulence.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#27 Laboratory results show WBC 15,000 (90% neutrophils) and no abnormal chemistries that are different from baseline.

Two blood cultures are drawn: one through the catheter and one percutaneously.

Vancomycin and piperacillin tazobactam are started.

On day 1 the patient remains stable, has a low-grade fever, but at 12 hours both blood cultures are growing gram positive cocci in clusters which are identified by a rapid test as MRSA.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#27 What would you recommend:

A) Attempt to retain the catheter and plan a course of IV vancomycin

B) Attempt to retain the catheter and plan a course of IV vancomycin plus IV gentamicin

C) Attempt to retain the catheter and plan a course of IV vancomycin plus use vancomycin lock therapy for 14 days

D) Remove the catheter and plan a course of IV vancomycin

E) Remove the catheter and plan a 7 day course of IV vancomycin plus 3 days of IV rifampin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#28 During a consult on an ICU patient with *Burkholderia cepacia* complex bacteremia, an intensivist mentions to you that it's their third patient with hospital-onset *Burkholderia cepacia* bacteremia that month.

The infection control team is alerted. They assess for commonalities between patients including rooms, providers, procedures, procedure locations, indwelling device types, medications, and patient care products.

Review was also undertaken of hand hygiene practices, environmental cleaning, and disinfection of devices used in multiple rooms.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#28 They noted the following:

1. The patients all occupied different rooms but were in the same ICU
2. All had been to CT scan in the week in the week before infection
3. All three patients had central lines placed by ultrasound on the unit. There was only one ultrasound machine for the unit but it was reliably wiped down with disinfectant wipes after every use.
4. Hand hygiene rates were high and environmental cleaning met hospital standards
5. Two of the patients were on heparin and a different two were on nebulized albuterol.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 2

#28 Which of the following is most likely to reveal the source of the cluster:

A) Culture the respiratory therapist's fingernails

B) Culture the heparin

C) Culture the albuterol

D) Culture the CT scanner

E) Culture the ultrasound gel

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#29 **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 tiny ticks from his body on an almost daily basis.

His exam is unremarkable except for fever.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#29 **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.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#29 **Which one of the following is another possible cause of his illness?**

A) Phlebovirus
B) Babesia
C) Scrub typhus
D) Rickettsia typhi
E) Adenovirus

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 2**

#30 **A 70-year-old woman presents with fever but without any other complaints: specifically she has no abdominal discomfort or diarrhea.**

Three of three blood cultures are positive for the same strain of Salmonella typhimurium.

What is the likely diagnosis?

A) Salmonella gallbladder carrier
B) Small bowel Salmonella infection
C) Intraabdominal abscess due to Salmonella
D) Salmonella arthritis
E) Salmonella Aortitis

18

Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

Dr. David Aronoff

18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Nocardia, Actinomycosis, Rhodococcus, and Melioidosis

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

6/21/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

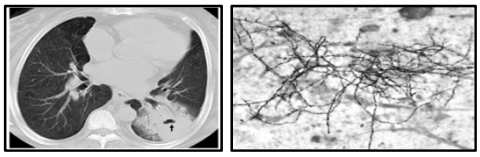
- **None**

Case

PREVIEW QUESTION

54 year old man with 4 weeks of cough, low grade fevers, & left-sided chest pain. Received a liver transplant 11 months ago, complicated by rejection, requiring high dose steroids 4 months ago. He receives TMP/SMX three times a week. On exam, he is stable, chronically-ill appearing, febrile (101.1ºF), has clear lungs and benign abdomen. Labs reveal a normal white blood cell count, slight anemia, & normal creatinine. Chest radiograph reveals hazy opacity in left lower lung zone. Chest CT reveals nodular air-space consolidation in the left lower lobe with central cavitation (image). Gram strain of bronchoalveolar lavage fluid reveals beaded gram positive filamentous organisms (image).

PREVIEW QUESTION



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

PREVIEW QUESTION

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

A. *Cryptococcus neoformans*
B. *Histoplasma capsulatum*
C. *Actinomyces israellii*
D. *Nocardia farcinica*
E. *Aspergillus fumigatus*

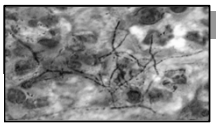
What are the most appropriate next steps in this patient's care?

A. Initiate therapy with intravenous TMP/SMX
B. Obtain a needle biopsy of the lung nodule to confirm the diagnosis
C. Obtain a brain MRI & start amikacin & TMP/SMX
D. Defer therapy until antimicrobial susceptibilities return

18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

Nocardia Infections



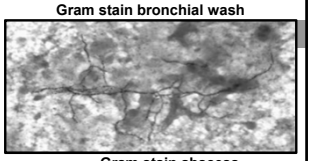
- **Microbiology:**
  - Beaded & branching gram-positive rods
  - Partially acid-fast
  - Aerobic (unlike anaerobic Actinomyces)
  - More than 80 species & >40 cause disease in humans
    - New phylogeny based on DNA sequence (*formerly*, *N. asteroides* complex): **species names are *lookups***.
- **Pathogenesis:**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

Photo: http://path.upmc.edu/cases/case226/dx.html; Good reference: Restrepo A & Clark NM. *Clinical Transplantation*. 2019;e13509.

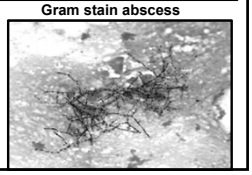
Images of *Nocardia*

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

Gram stain bronchial wash



Gram stain abscess



Images from http://thunderhouse4.uuu.blogspot.com/2010/06/nocardia-species.html

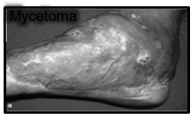
Clinical Features of *Nocardia*

- **Immunocompromised**
  - **Solid organ transplant**, hematopoietic transplant, chronic steroids, alcoholism, diabetes, CGD, CF, autoantibodies against GM-CSF, anti-TNF therapy, ectopic ACTH syndrome, AIDS (less common)
    - *PJP prophylaxis may not prevent nocardiosis*
  - Months to years after transplantation
- **90%**: **slowly progressive pneumonia** with cough, dyspnea, & fever
  - *Aspergillus* similar; co-infections occur
  - Similar to cryptococcal disease & actinomycosis
  - Can disseminate to any organ (**brain** in particular: **get MRI;** can be asymptomatic!)

Margalit I, *et al. Clinical Microbiology and Infection* (2021).

Clinical Features of *Nocardia*

- **10%**: Skin infections from direct inoculation:
  - Immunocompetent host in tropical region (*N. brasiliensis*)
  - Immunocompromised patient who gardens or walks barefoot
  - **Sporotrichoid** lesions
  - **Mycetomas**: chronic, progressive, lower limbs, draining sinuses (similar to Actinomycetes)

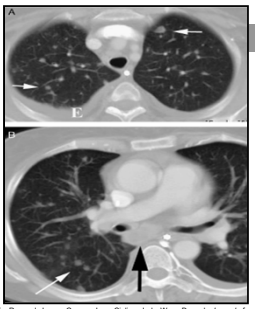


Baradkar V P, *et al. Indian J Pathol Microbiol* 2008;51:432-4 Sharma NL, *et al. Indian J Dermatol Venereol Leprol* 2008;74:635-40

Nocardia Diagnosis

- **Diagnosis**:
  - Suggestive **radiology**
    - Chest imaging: **nodules**, cavities, infiltrates with consolidation, effusions, ground-glass opacities
    - MRI brain: single or multiple **abscesses**
  - Blood **culture**, BAL, biopsy
    - Gram stain, modified acid-fast stain, culture
  - Species identification with nucleic acid sequencing or MALDI: **predictive of drug susceptibility**

- 56-year-old woman post kidney-pancreas transplant & *N. brasilienses*
- Small lung nodules (white arrows), small right pleural effusion & subcarinal lymphadenopathy (black arrow)

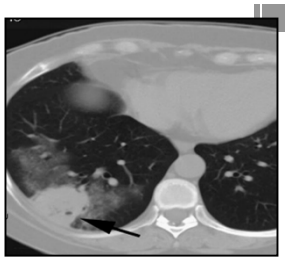


Pulmonary Nocardiosis: Computed Tomography Features at Diagnosis. Blackmon, Kevin; Ravenel, James; Gomez, Juan; Ciolino, Jody; Wray, Dannah. *Journal of Thoracic Imaging*. 26(3):224-229, August 2011. DOI: 10.1097/RTI.0b013e3181f45dd5

18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

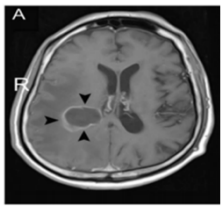
Speaker: David M. Aronoff, MD, FIDSA, FAAM

- 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

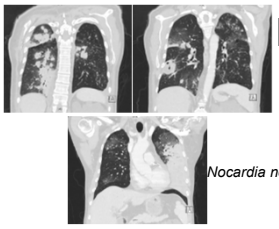
- Right frontoparietal subcortical ring lesion with a central dark signal & bright **ring enhancement** (black arrowheads) in postcontrast T1-weighted image.



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

Case

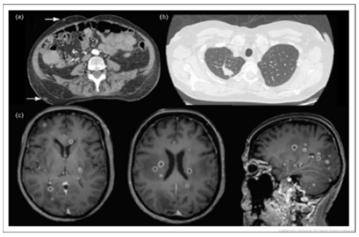
- July 2020: 60 YOM with history of PCKD s/p kidney transplant (12/2019) on immunosuppression, hypertension, & stroke presenting with 3 week of cough, fevers, dyspnea & malaise
- Ongoing cough & DOE x 4 months
- SARSCoV2 negative
- MRI head negative



Nocardia nova

1. Severe bilateral pneumonia with necrosis LUL & abscess in RLL
2. Many other areas of ground glass attenuation, consolidation, soft tissue nodules & tree-in-bud micronodules throughout
3. Small L>R pleural effusions & small pericardial effusion

Case



Nocardia cerradoensis

Total body CT & brain MRI of a solid organ transplant recipient with disseminated nocardiosis. (A) Sub-cutaneous nodules (white arrow) on CT-scan. (B) Nodule in the R upper lung seen on CT-scan. (C) Multiple round-shaped, contrast-enhanced lesions on gadolinium-enhanced T1-weighted brain MRI.

Lebeaux D, *et al. Current Opinion in Infectious Diseases* 34(6):611-618, December 2021.

Nocardia Treatment

- **Susceptibility testing**
  - 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)
- 2-6 weeks induction followed by 6+ months of oral TMP/SMX monotherapy

Restrepo A & Clark NM. *Clinical Transplantation*. 2019;e13509
Margalit I, *et al.* "How do I manage nocardiosis?." *Clinical Microbiology and Infection* (2021).

Nocardia Treatment

Antibiotics **2022**, *11*, 612

Table 3. Therapeutic management of nocardiosis according to clinical presentation.

Localization	Empiric Induction Treatment *,[a]	Maintenance Oral Therapy [a]	Duration
Primary skin Pulmonary stable	TMP/SMX orally Linezolid orally	TMP/SMXM 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. [a] 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)

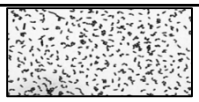
18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

Nocardia Buzzwords

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

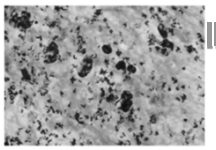
Rhodococcus



- **Clinical findings**:
  - Indolent pneumonia (80%) in **immunocompromised** host
  - **Fever, cough, hemoptysis**, fatigue, subacute, pleuritic CP
  - Nodules, thick-walled **cavities**, infiltrates, effusions possible
  - Extrapulmonary dissemination possible (**skin & brain**)
  - Mimic of TB, NTM, *Aspergillus*, *Nocardia*

Photo: microbe canvas

Rhodococcus



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

Image from W.V. Lin *et al. / Clinical Microbiology and Infection* (2019)

Rhodococcus

33 year-old HIV+ male (CD4 = 20) who lived on a cattle & horse farm

Presented to hospital with 1 month of fever, dry cough, 13# weight loss, sweats & anorexia

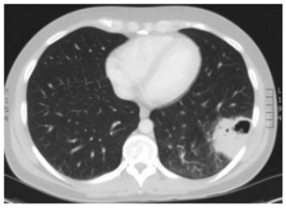


Image from Stewart A., *et al. IDCases.* (2019)

Rhodococcus

- **Diagnosis:**
  - **Culture** followed by 16S rRNA, MALDI-TOF
  - Tissue: gram stain, **necrotizing granulomatous** reaction; microabscess
  - Blood cultures may be positive (>25%)
- **Treatment:**
  - Combination therapy
  - 2 or 3 drug regimens: vancomycin + imipenem/meropenem + fluoroquinolone or rifampin 2-3 wks then oral FQ + azithro/clari or rifampin
    - Linezolid an alternative

Lin WV, *et al. Clin Micro Infect* (2019), Stewart A., *et al. IDCases.* (2019)

Rhodococcus Buzzwords

- **Short** Gram positive rod (coccobacillus)
- **Cavitary** pneumonia (hemoptysis)
- **Salmon pink** colonies
- Advanced **HIV**
- **Horse** / manure exposure

Case

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

- Which of the following would have been a likely source of this infection?

A. Hospital nebulizer while hospitalized in Australia (nosocomial superinfection)
B. Water or soil from his ranch
C. Coughing worker on his ranch
D. Sick sheep on his ranch.

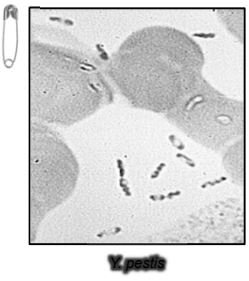
Melioidosis Take-Aways

- Microbiology lab:
  - Facultative intracellular gram-negative rod, *Burkholderia pseudomallei*
  - Oxidase positive
  - Characteristic bipolar staining with a "safety pin" appearance
- Typical patient:
  - SE Asia, northern Australia, South Asia (+ India), & China
    - *Esp.* Northeastern Thailand & northern Australia

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Bacteria with “safety pin” appearance

- *Yersinia pestis*
- *Vibrio parahemolyticus*
- *Burkholderia mallei & pseudomallei*
- *Haemophilus ducreyi*
  Ẽjua¡ jf£vl½
- *Klebsiella granulomatis*
  (granuloma inguinale)



Melioidosis Take-Aways

- **Clinical findings:**
  - **Acute** or chronic pneumonia or sepsis
  - Transmission via percutaneous inoculation, **inhalation**
  - Risk factors = **diabetes**, alcoholism, chronic renal & lung disease
  - Acute infection more common than chronic infection

Chakravorty A, Heath CH. *Australian Journal of General Practice* (2019)

Melioidosis Take-Aways

- **Clinical findings:**
  - Acute infection can present with **pneumonia, bacteremia & septic shock**
  - Metastatic abscesses: skin ulcers or abscesses more common than bone, spleen, brain, prostate
  - Chronic infection presents like TB (cough, hemoptysis, night sweats)
  - Can become latent & reactivate like TB (rare)

Wiersinga WJ, *et al. Nat Rev Dis Primers.* 2018

18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

Melioidosis Take-Aways

- **Diagnosis: Culture**
  - **Alert the lab you are concerned about this pathogen!**
- **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
  - **Meropenem or ceftazidime** then **tmp/smx for 3-6 months**

Wiersinga WJ, *et al. Nat Rev Dis Primers.* 2018
https://jcm.asm.org/content/54/12/2866
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2600349/

For the most up-to-date recommendations by the International Melioidosis Society: http://www.melioidosis.info

Melioidosis: **Buzzwords**

- **SE Asia** (Thailand)/Australia
- **Soil/water exposure** (inhalation/inoculation/rainy season; post-tsunami injury)
- Pneumonia + **severe sepsis**/shock or multiple abscesses
- Can be **years after exposure** (not usually)
- **Safety pins** on Gram stain; Gram negative rods

Le Tohic, s., *et al. European Journal of Clinical Microbiology & Infectious Diseases* (2019)

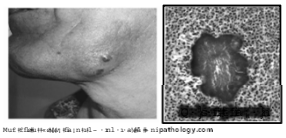
Glanders

- Caused by *Burkholderia mallei* & is rare in humans
- Requires close contact w/ infected animals (horses, donkeys, mules)
- Bacteria enter through the eyes, nose, mouth, or skin wounds
- *B. mallei* is an obligate mammalian pathogen & must cause the disease to be transmitted between hosts
- Africa, Asia, Middle East, Central America, South America
- Similar presentation to melioidosis

Smith ME, Gossman WG. Glanders And Melioidosis. [Updated 2017 Oct 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan.

Actinomyces Take-Aways

- Microbiology lab:
  - Gram-positive, **anaerobic**, non–spore-forming bacteria
  - Part of the normal mucosal flora of the oral, gastrointestinal, respiratory, & genital tracts
  - *Actinomyces israelii* most common species
  - Produce **sulfur granules**
- Typical patient:
  - Recent dental procedures
  - Aspiration (thoracic)
  - IUD (pelvic)

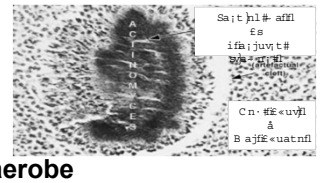


Actinomyces Take-Aways

- Clinical findings:
  - Oral-cervicofacial more common>abdominal & thoracic infection
  - **Lumpy jaw**
  - Slow growing mass, **ignores tissue planes**, can necessitate, form sinuses, fistulas
  - DDx: Cancer, TB, Nocardia
- Diagnosis:
  - Culture, histopathology (sulfur granules)
- Treatment:
  - **Penicillins** (PCN, ampicillin) x weeks to months

Actinomyces: **Buzzwords**

- **Sulfur granules**
- **Dental work**
- **IUD**
- **Erosive mass**
- **Filamentous anaerobe**

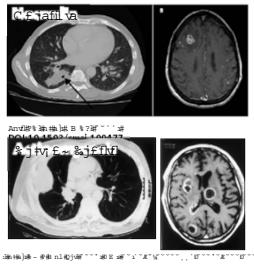


18 – Nocardia, Actinomycosis , Rhodococcus, and Melioidosis

Speaker: David M. Aronoff, MD, FIDSA, FAAM

Lesions in the **Lungs & Brain**

- Actinomycosis
- *Aspergillus, Zygomycetes*
- *Blastomyces, Coccidioides, Cryptococcus, Histoplasma*
- *Mycobacterium tuberculosis*
- *Nocardia*
- Infectious emboli (SBE)
- Lemierre syndrome (*Fusobacterium*)
- *Toxoplasma*
- Tumors



Causes of Sporotrichoid Lesions

Nodular lymphangitis

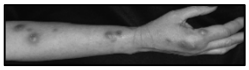


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Photo: eScholarship

THANK YOU

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19

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

Dr. Henry Chambers

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

Speaker: Henry Chambers, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

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

7/11/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Stock: Moderna**
- **Stock: Merck**
- **Data Monitoring Committee: Merck**

Topics for Discussion

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

Diagnosis of Endocarditis

Clinical Signs and Symptoms

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

Arch Intern Med. 2009;169:463-473

Q1. Which one of the following statements is correct?

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

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

Speaker: Henry Chambers, MD

Microbiology

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

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

Modified Duke Criteria for Diagnosis of Endocarditis

Definite pathologic diagnosis	**Definite Clinical Diagnosis**	**Possible Clinical Diagnosis**
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus	Two major criteria	Three minor criteria
OR	OR	OR
Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Five minor criteria	One major plus one minor criteria
	OR	
	One major plus three minor criteria	

If criteria either for definite or for possible endocarditis are not met, the diagnosis of infective endocarditis is rejected.

Duke Major Clinical Criteria for Diagnosis of Endocarditis

Positive blood cultures	**Positive Echocardiogram**	**Regurgitant murmur**
Typical microorganisms* from 2 separate blood cultures	Vegetation, defined as an oscillating	New
OR	intracardiac mass on a valve or supporting structure	(worsening old murmur does not count)
Persistently positive blood cultures (two > 12h apart, all of 3 or majority of ≥ 4)	OR	
OR	Abscess	
Single positive blood culture for Coxiella burnetii or phase I IgG antibody titer >1:800	OR	
	New partial dehiscence of a prosthetic valve	

**Staphylococcus aureus*, viridans group streptococci, *Streptococcus gallolyticus*, HACEK species (*Hemophilus* species, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, *Kingella*), and community-acquired enterococci in absence of a primary focus.

Duke Minor Clinical Criteria for Diagnosis of Endocarditis

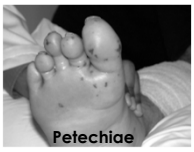
- Presence of predisposing cardiac condition or intravenous drug use
- Temperature ≥38.0ºC (100.4ºF)
- Vascular phenomena: systemic arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions
- Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
- Positive blood cultures that do not meet major criteria, OR serologic evidence of active infection with organism consistent with infective endocarditis

Modified Duke Criteria for Diagnosis of Endocarditis

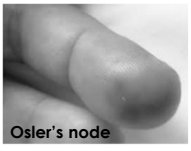
Definite pathologic diagnosis	**Definite Clinical Diagnosis**	**Possible Clinical Diagnosis**
Organisms on histology or culture of vegetation, intracardiac abscess or peripheral embolus	Two major criteria	Three minor criteria
OR	OR	OR
Evidence of a vegetation or intracardiac abscess, confirmed by histology showing active endocarditis	Five minor criteria	One major plus one minor criteria
	OR	
	One major plus three minor criteria	

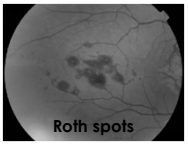
Sensitivity: 70% (definite), 95% definite + possible
Specficity: 95%

Microvascular/Immunologic Phenomena


Petechiae


Splinter hemorrhages


Osler's node


Roth spots

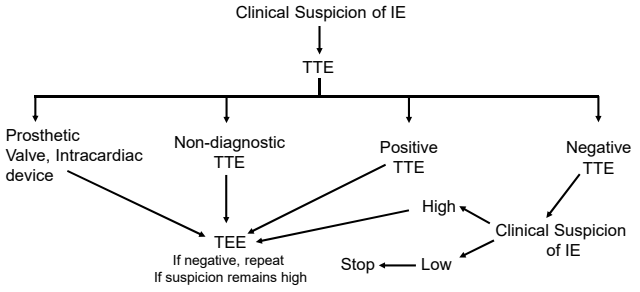

Subconjunctival hemorrhages


Janeway lesion

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

Speaker: Henry Chambers, MD

Role of Echocardiograpy



European Heart Journal (2015) 36, 3075–3123

Harmonic TTE vs TEE for Diagnosis of IE

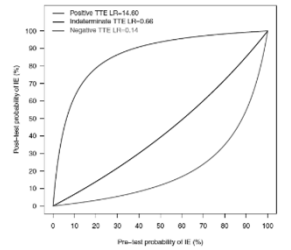


Figure 3 Utility of harmonic TTE in patients without prosthetic valves.

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

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

High Risk Factors for Proceeding to TEE

- High risk patients (examples)
  - Prosthetic valve
  - Congenital heart disease
  - Previous endocarditis
  - New murmur, heart failure, heart block, stigmata of IE
- High risk TTE (examples)
  - Large or mobile vegetations, anterior MV leaflet veg
  - Valvular insufficiency, perivalvular extension, valve perforation
  - Ventricular dysfunction

Native Valve Endocarditis

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

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

Speaker: Henry Chambers, MD

Native Valve Staph. aureus IE

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

No gentamicin, no rifampin

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

PREVIEW QUESTION

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

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

HACEK Organisms

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

Speaker: Henry Chambers, MD

Antimicrobial Therapy of HACEK Endocarditis

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

Oral Therapy of Endocarditis

Principles Of Antimicrobial Therapy

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

POET Trial of Oral Therapy

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

N Engl J Med 2019;380:415

Outcomes: POET Trial of Oral Therapy

1954 assessed for eligibility

↓

1554 excluded (428 no Duke criteria)

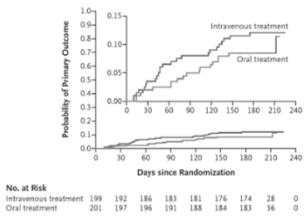
↓

400 randomized

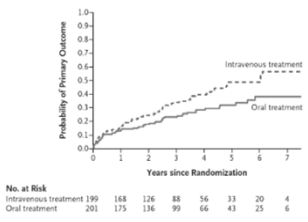
Outcome	IV (N=199)	PO (N=201)
Mortality	13 (6.5%)	7 (3.5%)
Unplanned surgery	6 (3.0%)	6 (3.0%)
Embolic event	3 (1.5%)	3 (1.5%)
Relapse	5 (2.5%)	5 (2.5%)

N Engl J Med 2019;380:415

Outcomes: POET Trial of Oral Therapy



N Engl J Med 2019;380:415



N Engl J Med 2019;380:1373

Culture-Negative Endocarditis

Culture-Negative Endocarditis

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

Culture-Negative Scenarios

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

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Tools for Diagnosis of Culture-Negative Endocarditis

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

Prosthetic Valve and Device-Related Endocarditis

Microbiology of PVE

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

Adapted from Karcher and Chu, UpToDate, 2020

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

Speaker: Henry Chambers, MD

Diagnosis of PVE

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

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

Mycobacterium chimaera PVE

- Culture-negative endocarditis
- Indolent, may occurs years after cardiac surgery
- Due to contamination of heater-cooler units (Sorin Stockert 3T; LiveNova PLC, London, UK) connected to cardiac bypass machines

Antimicrobial Therapy of PVE

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

Cardiac Implantable Device Infections

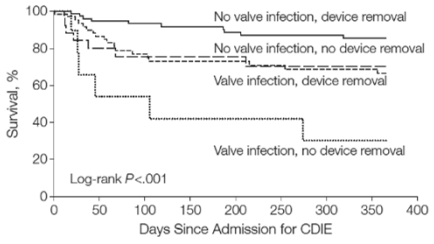
(permanent pacemakers, defibrillators)

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

Cardiac Implantable Device Infection Types

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

Survival with and without Device Removal

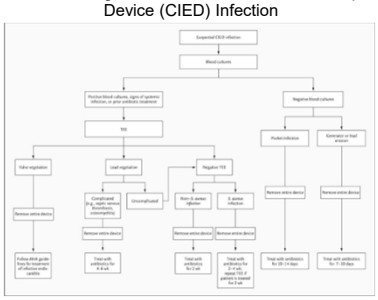


Athan, JAMA. 2012; 307:1727-1735

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

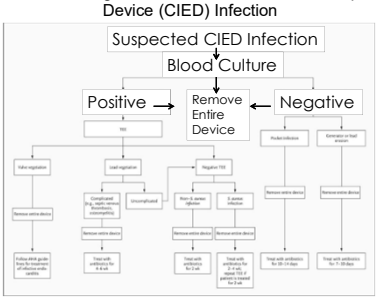
Speaker: Henry Chambers, MD

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



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

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



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

AHA Guidelines for Management of Cardiac Implantable Device Infections

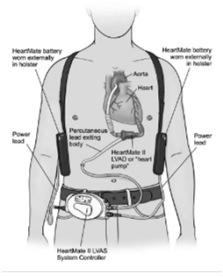
- Blood cultures before antibiotics
  - If positive, then TEE
- Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (conside for bacteremia with other endocarditis-causing organisms)
- Therapy (antibiotic based on susceptibility)
 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

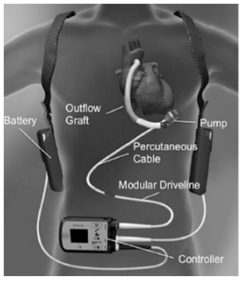
Circulation 2010;121:458-77

AHA Guidelines for Reimplantation

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

Infection of Ventricular Assist Devices





Types of VAD Infections

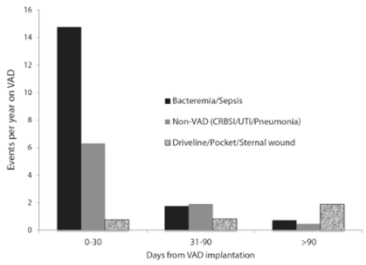
- VAD-specific infections
  - Pump pocket/cannula infections
  - Pocket infections
  - Driveline exit site infections (superficial or deep)
- VAD-related infections
  - Bloodstream infections (VAD-related, IV catheter/non-VAD related)
  - Endocarditis (pump or cannula, native valve)
  - Mediastinitis, sternal wound infections
- Non-VAD infections

Clinical Transplantation 2019;33:e13552.

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

Speaker: Henry Chambers, MD

Timing and Types of Infections After VAD Implantation



Clinical Transplantation 2019;33:e13552.

Microbiology of VAD-Specific Infections

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

Clinical Transplantation 2019;33:e13552.

Management and Therapy

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

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

Antimicrobial Therapy

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

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

Other Management Issues

Case Presentation

- 52 yo M admitted from the ED with fever, chills, abdominal pain for 3 days
- PMH: HCV, cirrhosis, varices, injection drug use
- T 40.6°C, HR 127, BP 125/88, no murmur; combative, disoriented, nuchal rigidity, nonfocal neuro exam

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

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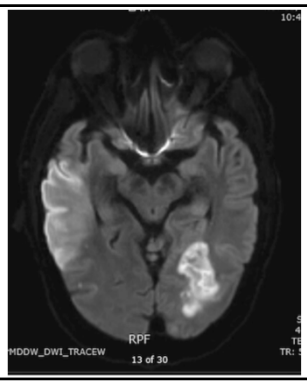
Initial Work-Up

- WBC 15K; Na+ 127, rest of BMP normal
- CSF: 388 white cells, 95% PMNs, Pro 71, Glu 69, Gram stain no organisms, culture positive for MRSA @ 18h
- CT abd: splenic infarcts
- CT head: without contrast: no blood & otherwise negative
- TTE: Thickened AV, mild AR, mild MR, possible R coronary cusp vegetation
- Rx: Vancomycin + ampicillin + ceftriaxone, then vancomycin



Hospital Course

MRI: Numerous areas of restricted diffusion in multiple vascular territories most notably in the L occipital lobe and R temporal lobe

Blood cultures persistently positive; CSF 19 WBCs and sterile

HD5: cold, pulseless RLE; heparin is administered, he is taken to the OR for thrombectomy and has a fatal cardiac arrest post-op

Embolic Events in IE

- Systemic embolization up 30-40%; CNS accounts for about half
- Highest rates in MV IE (anterior > posterior leaflet)
- 50% identified at presentation, prior to therapy
  - ~65% of the remainder during first 2 weeks of antibiotic therapy
  - ~3% suffer a stroke after 1 week of therapy (benefit of early surgery correspondingly less)
- Value of CNS imaging all patients with IE unknown, may be considered as part of pre-op evaluation
- Preventative systemic anticoagulation, antiplatelet therapy contraindicated (guidelines do not address anticoagulation for large, non-CNS emboli)

Anticoagulation

- Management is controversial
- Discontinue all forms of anticoagulation in patients with a mechanical PVE and a CNS embolic event for 2 weeks
  - Reinstitute heparin first then carefully transition to warfarin
- Aspirin or other antiplatelet agents as adjunctive therapy is not recommended
- Continuation of long-term antiplatelet therapy in IE with no bleeding complications may be considered
- Thrombolytic therapy not recommended

Surgical Management of NVE

- Optimal timing of surgery not known
- Early surgery (no standard definition)
  - Heart failure due to valvular dysfunction, fistula, shunt
  - Uncontrolled infection
    - MDR, fungal pathogens, persistently pos. BC (5-7d)
    - Paravalvular complication (abscess, heart block, fistula)
  - Prevention of systemic embolization
    - Vegetation > 10 mm, one or more embolic events on therapy

Valve Surgery with Stroke

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

Am Heart J 2019;216:102-112

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

Speaker: Henry Chambers, MD

Pan-Scanning

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

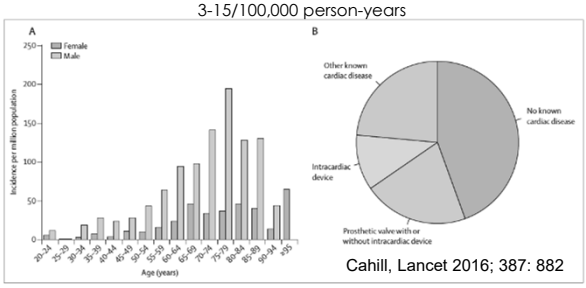
Fever during Therapy of Endocarditis

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

Back-up Slides

Epidemiology

3-15/100,000 person-years



Cahill, Lancet 2016; 387: 882

Transcatheter Aortic Valve Replacement

- Enterococci > S. aureus/CoNS > streptococci
- Risk of PVE for TAVR similar to surgical aortic valve replacement (SAVR)
- Sensitivity of TEE probably less in TAVR compared with SAVR
- Higher early and 1-year mortality with TAVR than SAVR, likely due to patient selection
- Antimicrobial therapy as for PVE

Clin Infect Dis 2021; 72:1687; PlosOne 2020;15: e0225077;
Clin Microbiol Infect 2020;26:999

Thanks

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Zoonoses

Dr. David Aronoff

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Zoonoses

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John B. Hickam Professor of Medicine
Chair, Department of Medicine
Indiana University School of Medicine

6/14/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Zoonoses: major infection route from animals in USA

- Most recent epidemics & pandemics have been caused by zoonotic pathogens
- Emerging coronaviruses, haemorrhagic fever viruses, arboviruses, influenza A viruses & bacteria have caused recent major zoonotic epidemics

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)

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.
Mycobacteriosis	*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*

CATS
- *Bartonella henselae*
- *Pasteurella multocida*

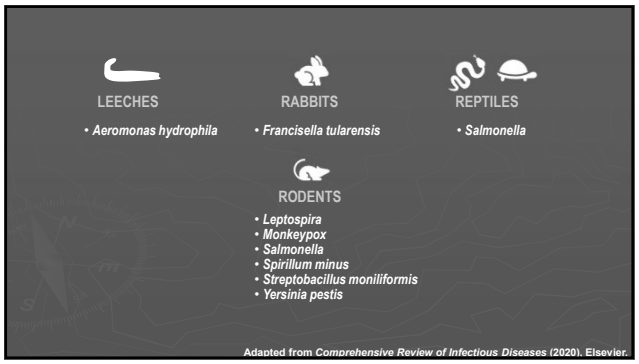
BIRDS
- *Chlamydia*
- *Chlamydophila psitacci*

FARM ANIMALS
(sheep, cows, goats, chicken, *etc*)
- *Bacillus anthracis*
- *Brucella*
- *Coxiella burnetii*
- *Campylobacter*
- *E. coli* (Shiga toxin+)
- *Erysipelothrix rhusiopathiae*
- *Hepatitis E*
- *Leptospira*
- *Salmonella*

FISH
- *Erysipelothrix rhusiopathiae*
- *Mycobacterium marinum*
- *Streptococcus iniae*
- *Vibrio*

DOGS
- *Campylobacter*
- *Capnocytophaga*
- *Leptospira*
- *Pasteurella multocida*
- *Staph intermedius/pseudintermedius*

Adapted from *Comprehensive Review of Infectious Diseases* (2020), Elsevier.



Zoonoses: major infection route from animals in USA

- **Direct contact with animal or animal tissue**
  - Cat scratch disease, anthrax, tularemia, monkeypox
- **Contact with insect vector**
  - Tularemia, plague
- **Intact skin contact with animal urine**
  - Leptospirosis
- **Ingestion of animal product**
  - Brucellosis
- **Inhalation of animal product**
  - Q Fever

Direct contact with animal or animal tissue

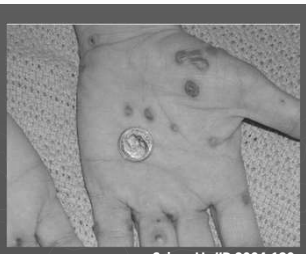
Question #1

19 yr woman presented with several days of headache, fever, chills, myalgias, cough & a rash

On exam she had generalized adenopathy & a vesiculopustular rash with focal areas of hemorrhage progressing in a uniform manner including the entire body, most prominently on the trunk, palms & soles

She reported her new pet prairie dog was also ill (lethargy, wasting, not eating)

Question #1



Sejvar JJ, *JID* 2004:190

Question #1

What is the most likely infection?

A. *Erysipelothrix rhusiopathiae*
B. Smallpox
C. Gambian cutaneous ulcerans
D. Monkeypox
E. Yaws (*Treponema pallidum pertenue*)

Question #2

25 yr male presented in July with painful right inguinal mass of one week's duration. He is otherwise well. Married. Monogamous. No hx penile or skin lesion. Fishing last week in Northern Virginia creek, hiked through wooded area. Picked ticks off legs & neck. Has kitten & dog. Exam: T37°C, 5 cm tender red mass in right midinguinal area, fixed to skin. Genitalia normal. Aspiration of soft center: 5 cc yellow pus. Gm stain neg. cephalexin 250 mg qid. One week later: mass unchanged. Culture neg. Syphilis FTA & HIV neg.

Question #2

Most likely dx:

A. *Bartonella henselae*
B. *Treponema pallidum*
C. *Haemophilus ducreyi*
D. *Francisella tularensis*
E. *Klebsiella (Calymmatobacterium) granulomatis*

Purulent inguinal node

- *Bartonella henselae*: young cats
  - **Stellate abscess** on bx. **Warthin Starry** stain positive early
  - Dx: serology, PCR, or DFA on pus
- Tick borne tularemia ("glandular"): this case *could be* tularemia
  - Exposure to wild animals or their ticks
  - Gram stain, routine culture negative
  - But: he should be **systemically ill** (fevers, chills, malaise common)
  - **Uncommon**: 100-200 cases per year in the USA
- Chancroid: painful genital ulcer
- No suppurative lymph nodes in syphilis or granuloma inguinale (*Klebsiella granulomatis*) (painless ulcers)

Suppurative inguinal lymph nodes (continued)

- *Staphylococcus aureus*. Gram stain of pus & culture positive. Distal lesion may be present.
- Lymphogranuloma venereum (LGV)-
  - Sexually transmitted
  - *Chlamydia trachomatis* L1-L3: genital lesion usually inapparent
  - "Stellate abscesses" on bx
  - (+) Nucleic acid amplification test on urine or wound

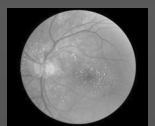
Cat Scratch Disease

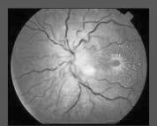
- *B. henselae* causes most cases
- >13,000 cases in the USA per year[1]
- Clinical findings:
  - 80% <21 yrs old, acute suppurative lymphadenitis proximal to bite, scratch, lick of young cat
  - Cats have chronic bacteremia but seem healthy
- Cat fleas may transmit between cats & occasionally to humans

1. Nelson CA, *et al. Emerging Infectious Diseases* 22 (2016). Photo from http://www.catscratchmed.com

Cat Scratch Disease

- Papule or pustule often at inoculation site if sought
- Often self-limited
- Encephalitis, **stellate retinitis**, uveitis rare





Lipid exudates forming a macular star

Photos from http://www.catscratchmed.com, http://imagebank.asrs.org/file/1173/cat-scratch-retinitis-with-macular-lipid, http://www.nejm.org/doi/full/10.1056/ENEJMicm010038#t=article

Cat Scratch Disease

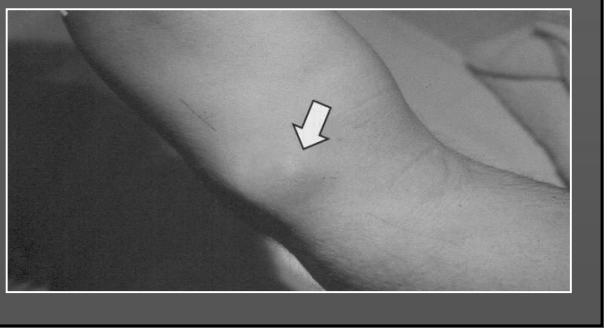
Rx: 10% drain spontaneously

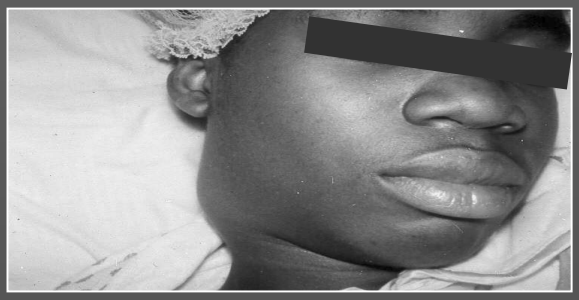
If not, node aspiration improves pain & helps exclude *Staph. aureus*

Treatment = AZITHROMYCIN x 5 d

(TMP/SMX, clarithromycin, ciprofloxaxin or rifampin as alternatives)

Treat to prevent serious complications, since up to 14% of patients will have dissemination, with potential infection of the liver, spleen, eye, or CNS





Warthin Starry silver stain

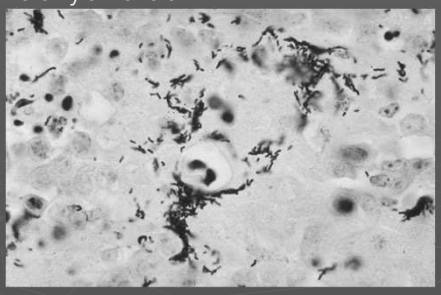
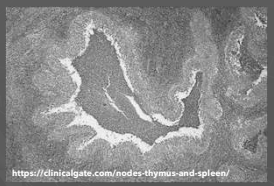


Photo by Andrew Margileth, MD., from http://emedicine.medscape.com/article/214100-workup#c8

Cat Scratch Lymphadenopathy
Stellate abscesses, necrotizing granulomas
Necrotic area with neutrophils surrounded by **palisading histiocytes**



https://clinicalgate.com/nodes-thymus-and-spleen/

Lymph nodes showing central abscess formation surrounded by palisaded histiocytes

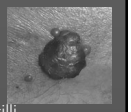
https://basicmedicalkey.com/cat-scratch-disease/

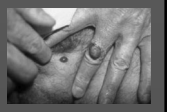
Major Syndromes due to *Bartonella* species

- *Bartonella*: **Slow growing** weakly Gram (-) rod
- *B. henselae*- cat scratch disease, peliosis
- *B. bacilliformis*- the **Andes, Peru** & **sand fly** bite; Carrion's disease
  - Oroya fever (acute phase: fever + anemia) → verruga peruana (later; hemangioma-like nodules in the skin & mucous membranes); Treatment = ciprofloxacin (Oroya); azithromycin (vp)
- *B. quintana*
  - Human **body louse** *Pediculus humanus var. corporis* = vector
  - Bacteremia in persons experiencing **homelessness**, trench fever
  - **Endocarditis**

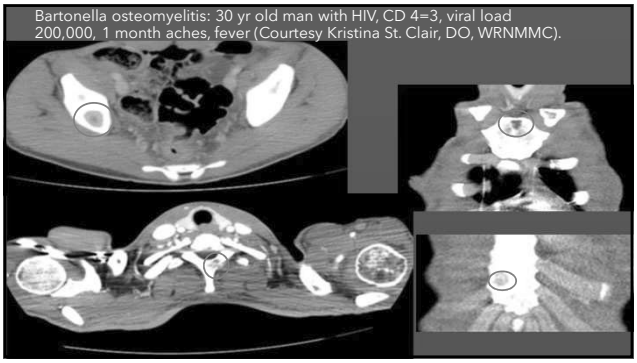
Major Syndromes due to *Bartonella* species

- HIV-associated (CD4<<100)
  - **Bacillary angiomatosis** (cutaneous)
    - Caused by either *B. henselae* or *B. quintana*
    - Lesions bleed easily
    - Biopsy: vascular proliferation, plump endothelial cells, bacilli
    - DDx = Kaposi sarcoma
  - Bacillary **peliosis** (*B. henselae*)
  - Osteomyelitis (lytic; *B. quintana*)
  - Chronic bacteremia/endocarditis





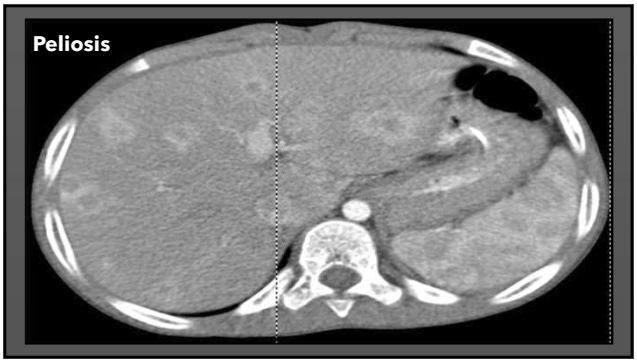
Images from http://mddk.com/bacillary-angiomatosis.html

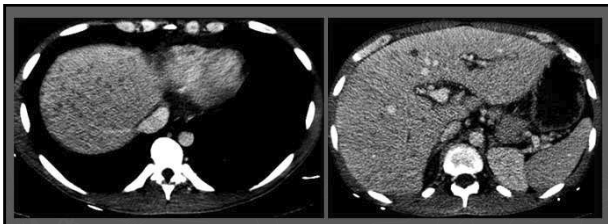


Bartonella osteomyelitis: 30 yr old man with HIV, CD 4=3, viral load 200,000, 1 month aches, fever (Courtesy Kristina St. Clair, DO, WRNMMC).

Bacillary peliosis

- *B. henselae*
- Hepatosplenic bacillary peliosis
- Fever, chills, hepatosplenomegaly
- CT: Hypodense dense center +/- contrast enhancing rim
- Ultrasound, MRI = masses
- Blood filled spaces. Numerous bacilli on Warthin Starry stain or immunostaining





29 year old male with longstanding HIV (CD4 < 10) with 3 months of fevers & weight loss. + hepatosplenomegaly & mild transaminitis, elevated Alk phos. CT showed innumerable hepatic & splenic hypodensities. IgG (+) *Bartonella* 1:512 & serum *Bartonella henselae* PCR (+). He had rescued a kitten 6 months prior & reported scratches & bites.

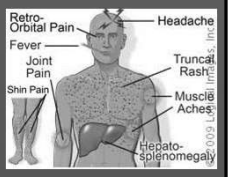
Case courtesy of Dr. Sam Bailin (Vanderbilt)

Solid Organ Transplantation

- SOT, like AIDS, can predispose to ALL the manifestations of bartonellosis
  - Lymphadenitis
  - Skin lesions (bacillary angiomatosis)
  - Bone lesions
  - Liver lesions

Bartonella quintana

- Transmitted by human body **lice**
- Crowded, unsanitary conditions: "trench fever" in WW1
- Splenomegaly, fever, arthropathy & arthritis, leg pains, rash, & severe weakness, thrombocytopenia
- Bacteremia, endocarditis in AIDS, **homelessness** +/- alcoholics

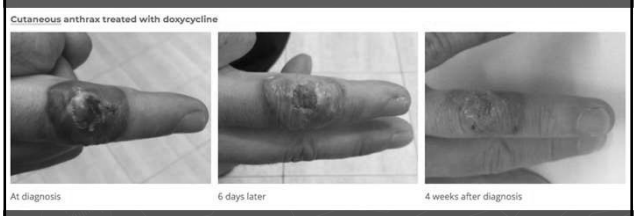


Brouqui P, *et al. NEJM* (1999)

Bartonella endocarditis

- <5% of all bacterial endocarditis
- Consider *B. quintana* or *B. henselae* in **homelessness** & with **culture negative** endocarditis
- Insidious or acute onset of fever, weight loss, anorexia.
- Serology: IgG>1:800 highly suggestive (not species specific)
- **PCR** of serum, valve tissue
- Lysis-centrifugation blood cult.
  - 35ºC, fresh chocolate agar, hold 2-4 weeks
- Rx: gentamicin + doxycycline x 6 weeks

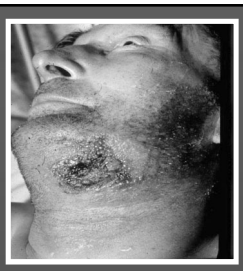
ANTHRAX



Images from https://www.dermnetnz.org/topics/anthrax

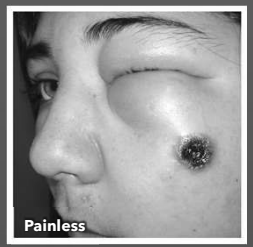
ANTHRAX

- Skin (95%): pruritic papule on skin exposed to goat hair, animal hides. Small **vesicles around an ulcer**. +/- pain. **Edema**. Mild systemic symptoms.
- DX: *Aerobic*, encapsulated, sporulating **Gram positive** bacillus seen on smear, culture of vesicle fluid
- RX: Penicillin but "weaponized" strains resistant to multiple antibiotics
- Inhalation (5%), ingestion (<1%)
- Anthrax rare in USA. Bioterrorism: see online lecture



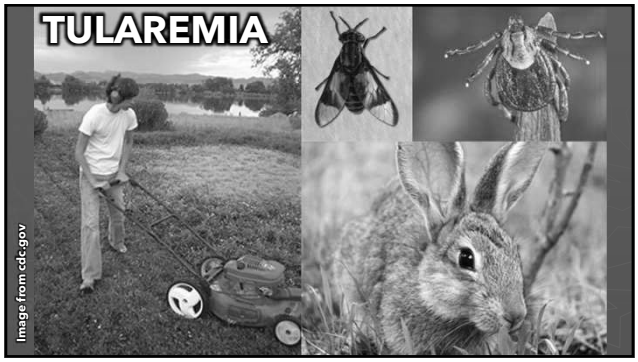
http://www.pcds.org.uk/clinical-guidance/anthrax

Edema
Vesicles
Necrotic ulcer



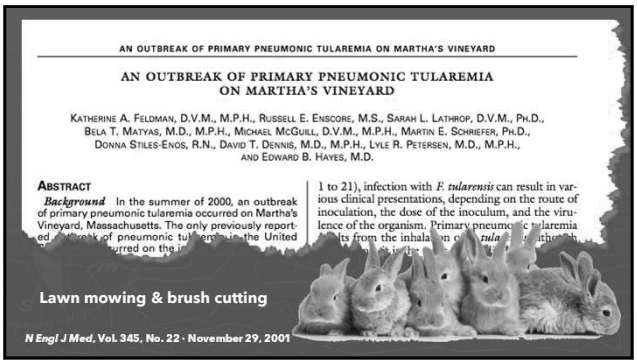
https://www.nejm.org/doi/full/10.1056/NEJMicm0802093

TULAREMIA



TULAREMIA

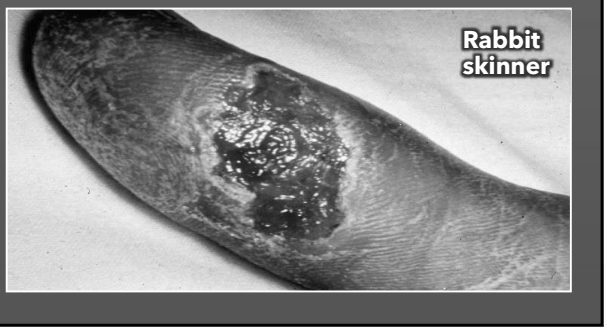
- Highly infectious gram-negative **coccobacillus** *Francisella tularensis*
- Vectors = **Ticks** (*Dermacentor variabilis* > *Amblyomma americanum*) & **Deerflies**
- Direct inoculation = rabbits, squirrels, muskrats, beavers, cats
- Hunters **skinning animals** (old days); farmers, veterinarians
- Red tender local lymph node inoculation site may form ulcer
- **Ulceroglandular >** glandular >> oculoglandular, pharyngeal, typhoidal, pneumonic = Bioterrorism, landscapers, mowers



TULAREMIA

- Incubation period: 3-5 days but up to 3 weeks
- DX: Serology; PCR
- Culture of *F. tularensis* is lab hazard. Neg routine culture, needs chocolate agar
- RX: **gentamicin** (or streptomycin), **FQs**, **doxycycline**
- Prophylaxis (bioterrorism) doxycycline

Maurin & Gyuranecz. *Lancet* (2016)



Glandular Tularemia

68-year-old with 1 wk fever then 2 mo progressive, painful swelling on R. side of neck

Exposure to a sick cat

Diagnosis made by + IgM (1:1280)

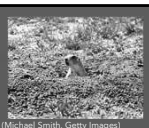
Improved with 4 wk doxycycline

Marks, Laura, and Andrej Spec. "Glandular Tularemia." *New England Journal of Medicine* 379.10 (2018): 967-967.

Contact with insect vector

PLAGUE

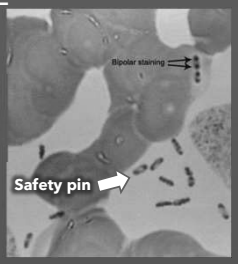
- *Yersinia pestis*
- New Mexico, California, Arizona & Colorado
  - Rodent **flea bite**
  - **Prairie dogs**
- Fever, nausea & swollen, painful lymph nodes
- Sepsis, pneumonia-hematogenous or aerosol in crowded conditions

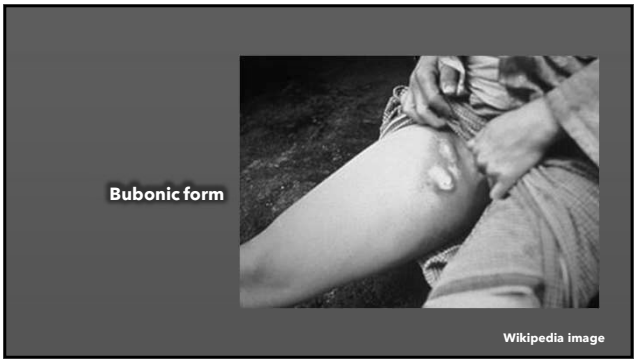

(Michael Smith, Getty Images)

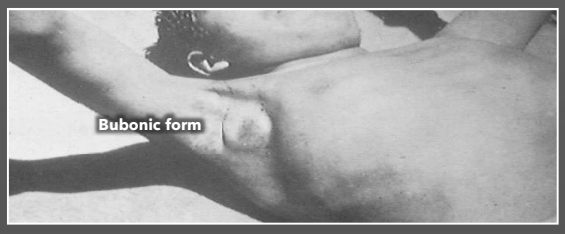

(Eye of Science/Science Source)

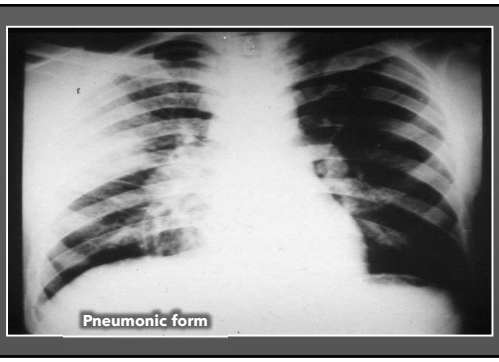
PLAGUE

- Gram negative coccobacillus
- **Bipolar-staining** bacilli
- **Safety pin** appearance
  - *Yersinia pestis*: lab hazard
- Treatment: **Streptomycin** >> doxy, cipro









Large Outbreak in Madagascar

Plague is an endemic disease in Madagascar

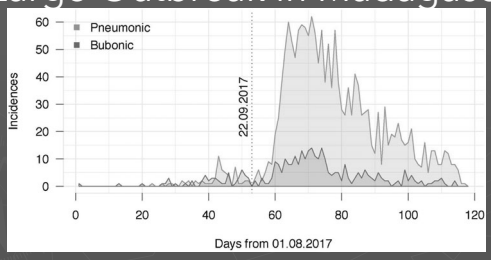
Each year there is a seasonal upsurge between September – April

In 2017, an unprecedented pneumonic plague outbreak hit the main island

Nearly 2,500 reported or suspected cases (78% pneumonic)

https://www.sciencedaily.com/releases/2019/04/190416132101.htm
Randremanana R, *et al. Lancet ID*, 19(5) (2019)
Majumder MS, *et al. PLoS Curr.* (2018)

Large Outbreak in Madagascar



Nguyen VK, *et al. Epidemics* (2018)

2019

Mongolian Couple Die of Plague after Eating Raw Marmot

THE INCIDENT SPARKED A QUARANTINE, STRANDING TOURISTS FOR DAYS

May 17, 2019

By Jonny Lupsha, News Writer

A couple in Western Mongolia have died of bubonic plague after eating raw marmot, *The Guardian* reported. There are people who believe eating the innards of the rodent is good for their health. Although people ignore health warnings not to eat uncooked meat, raw marmot can carry the plague germ *Yersinia pestis*. Plague is known for causing the Black Death in the 14th century—but was it that simple?

Intact skin contact with animal urine

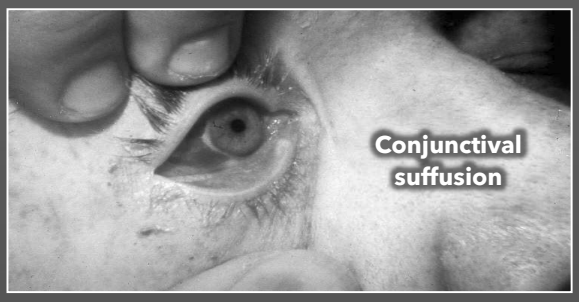
Question #3

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

Question #3

Most likely diagnosis:

A. malaria
B. dengue
C. ehrlichiosis
D. leptospirosis
E. Zika



Ingestion of animal products

Question #4

A 41 year old car salesperson from Baltimore was admitted for a febrile illness & found to have *Brucella melitensis* in their blood culture. They had attended a dinner a month prior where some family members from Greece had brought food from home. About two weeks prior to onset of fever, they had bought some lamb & beef at a farmer's market outside Baltimore.

Question #4

The most likely source of the brucellosis was which of the following:

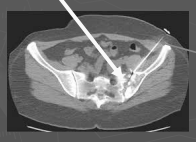
A. Home made sausage from Greece
B. Home made goat cheese from Greece
C. Cole slaw from a Baltimore delicatessen
D. Beef tartar, meat from the farmer's market
E. Lamb kabobs, meat from the farmer's market

BRUCELLOSIS

- Exposure to non-USA dairy or meat, **unpasteurized** cheese, uncooked meat,
- Slaughterhouse worker, meat packer, veterinarian
- Acute or indolent onset fever, aches
- Nodes, liver, spleen may be enlarged

BRUCELLOSIS

Later onset lesions in <u>bone</u>, liver
Epididymo-orchitis[1], endocarditis
sacroiliitis, tenosynovitis, meningitis



Biopsy needle

Malodorous perspiration (uncommon) "pathognomonic"[2]

1. Ip CCK, *et al. BMJ Case Rep* 2019;12:e230007. doi:10.1136/bcr-2019-230007
2. 2. Pappas G, *et al. NEJM* (2005)

BRUCELLOSIS (con't)

- WBC normal or low, anemia, plt can be low
- DX: Bone marrow/blood/tissue culture, serology, PCR
- RX: Doxy plus rifampin or strep/gent
  - TMP-SMX in pregnant or young children

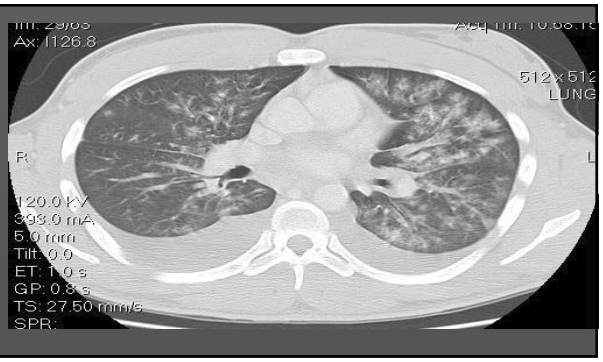
Inhalation of animal products

Case

- A 22 year old previously healthy male contractor returned from Afghanistan one week prior to presentation. He had a three day history of fever, myalgia, arthralgia, mild headache & cough. He had vomited once & had mild midepigastric, nonradiating pain.
- The facility he was hired to guard was adjacent to the path that the local sheep & goat herders used on their way to market & he had purchased a wool rug from one of the locals. He remembers shaking it hard to get rid of the dust.
- He reported that some members of his guard unit also had flu-like illness from which they recovered without treatment.

Case

- Examination was normal except for a variable temperature up to 102°F
- WBC **3.3**K, platelets **121**K, creatinine 1.2, AST **144**, ALT **154**, alk phos 88, total bilirubin 0.6
- Admission chest Xray was normal
- Ceftriaxone was begun but the patient remained febrile & had the chest CT shown on the next slide

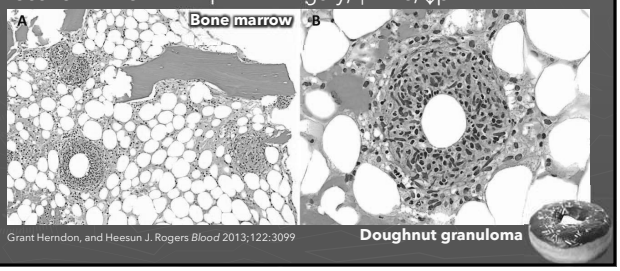


Question #5

Which of the following is the most likely diagnosis?

A. brucellosis
B. anthrax
C. leptospirosis
D. Q fever
E. Visceral leishmaniasis

A 54-year-old man with a history of multiple myeloma presented with intermittent fevers, chills, fatigue, & weight loss for 1 month. +splenomegaly, ↑LFTs, ↓plt



Grant Herndon, and Heesun J. Rogers *Blood* 2013;122:3099

Rat Bite Fever

- Rat-bite fever (RBF): infection caused by 2 different bacteria:
  - *Streptobacillus moniliformis*, the only reported bacteria that causes RBF in North America (streptobacillary RBF): fever, chills, myalgia, headache, & vomiting; rash
    - Gram negative; can culture
  - *Spirillum minus*, common in Asia: fever, ulceration at the bite site, lymphangitis, lymphadenopathy, distinct rash of purple or red plaques
    - Darkfield needed to diagnose; culture negative
- Most infected after contact with rodents carrying the bacteria
  - Consumption of food or water contaminated with the urine & droppings of rodents carrying the bacteria.
- Penicillin treatment

https://www.cdc.gov/rat-bite-fever/index.html

QUICK SUMMARIES

Summary of Key Exposures

- Flea bites from rodents or outdoor cats in contact with wild rodents:
  - *Yersina pestis* PLAGUE (New Mexico, Colorado, Arizona)
- Wild game or their ticks: handling, cleaning muskrats, beavers, rabbits, squirrels
  - TULAREMIA

Summary of Key Exposures

- Eating unpasteurized cheese from overseas, including goat cheese:
  - BRUCELLOSIS
  - Unpasteurized queso *could suggest* ***Listeria***
    - Stem likely to include pregnant patient

Summary of Key Exposures

- Animal **urine** on intact skin: hiker, farmer, forestry, veterinarian, swimming, falling in water or rafting in contaminated water
  - **Leptospirosis**
- Handling overseas animal **hair**, **hides**
  - **Anthrax**
- Slaughterhouses, veterinarians, parturient cat exposure, sheep handlers, living downwind of sheep/cattle farms
  - **Q Fever**

Key Clinical Syndromes

Culture negative endocarditis
- Homelessness: *Bartonella quintana*
- Animal exposure: *Coxiella burnetii*

Kaposi-like skin lesions: *Bartonella henselae*
Tender lymph node: bartonellosis, tularemia, plague
Fever + jaundice: leptospirosis
Sacroiliitis or chronic illness w/ stinky sweat: brucellosis
Rat bite in US: *Streptobacillus moniliformis*
Rat bite in Asia: *Spirillum minus*

Other Zoonoses

- There are many zoonoses
- Be sure to review them before the boards

Chikeka & Dumler *Clin Microbiol Infect* 2015; 21: 404-415

The End

Thank you!

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21

Staphylococcal Disease

Dr. Henry Chambers

21 – Staphylococcal Disease

Speaker: Henry F. Chambers, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Staphylococcal Diseases

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

7/11/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Stock: Moderna**
- **Stock: Merck**
- **Data Monitoring Committee: Merck**

Outline of the Talk

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

IDBR 2022 PREVIEW QUESTION

Q1. 45 year old man, one week of back pain. He is afebrile and vital signs are normal; normal exam except for tenderness to palpation of the lower back. MRI shows L3-L4 discitis, hyperemic marrow; 1 of 3 blood cultures is positive for coagulase-negative staphylococci.

Which one of the following would you recommend?

A. Bone biopsy with culture as the blood isolate is likely a contaminant
B. Request speciation of the blood isolate
C. PET-CT to look for another focus of infection for biopsy
D. Fungal serologies, PPD

Staphylococcus lugdunensis

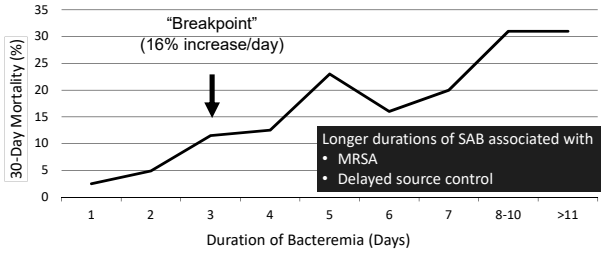
- Coagulase negative….
  - The tube "free" coagulase test is negative
  - The latex "bound" coagulase (i.e., clumping factor) test may be positive and confuse physicians
- Virulent, aggressive, similar to *S. aureus*.
  - Bacteremia, NV and PV endocarditis
  - Bone and joint infection
  - Pacemaker, other device-related infections
- Susceptible to many antibiotics (5-10% *mecA* positive)

Risk factors for poor outcome, complicated S. aureus bacteremia

Q2. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia?

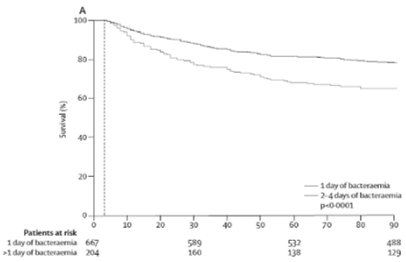
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

Longer durations of Staph. aureus bacteremia (SAB) are associated with higher the mortality



Clin Infect Dis. 2020; 70:566-573

Even 2 days of Bacteremia on Therapy is Bad



Lancet Infect Dis 2020; 20: 1409

Echocardiography

Q3. A single positive blood culture for Staph. aureus…….

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

Prediction Scores to Rule Endocarditis (and avoid an ECHO)

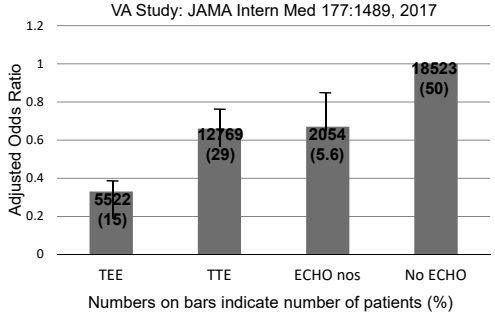
POSITIVE (Cutoff >4)	PREDICT (Cutoff ≥2)	…toff ≥3)
TTP < 9h – 13h (2,3,5)	ICD (2)	…boli (5)
IVDU (3)	Pacemak…	Meningitis (5)
Vascular phenomena (6)	CA…	Intracardiac device (4)
Predisposing heart dis (5)	…BC > 72h (2)	Previous IE (3)
		IVDU (4)
		Positive BC > 48h (3)
		CA or HCA SAB (2)
		Sepsis or septic shock (1)
		CRP > 190 mg/L (1)

Prevalence of endocarditis 12%-18% overall
Prevalence of endocarditis with a negative score 2.2-4.9%

Clin Infect Dis 2022;74:1442, J Antimicrob Chemother 2022; 77: 2003, J. Clin. Med. 2022; 11: 1502.

ECHO and Mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

Role of Echocardiography for S. aureus Bacteremia

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

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

Single positive blood culture for S. aureus

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

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

Treatment of MSSA Bacteremia

IDSA 2022 PREVIEW QUESTION

Q4. On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia the patient has developed new neutropenia (1,000 neutrophils). MICs (µg/ml) of the blood isolate are penicillin 0.12 (S), cefazolin 0.5 (S), vancomycin 1 (S), daptomycin 0.5 (S), ceftaroline 0.5 (S).

Which one of the alternative agents would you recommend?

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

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

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

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

Clinical Infectious Diseases 2021;73(9):1650

Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

…the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable.

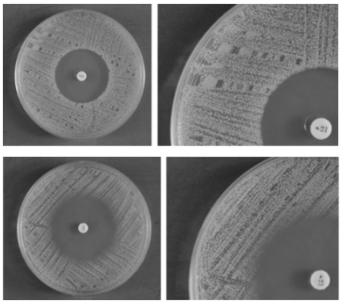
Pen MIC (µg/ml)	No. (%) of strains Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

Negative

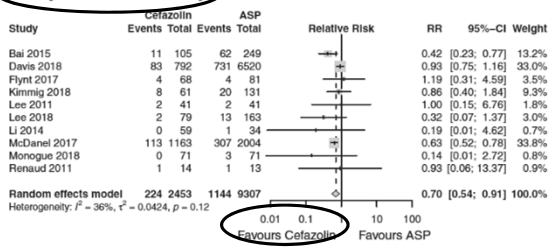


MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

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

Cefazolin vs Anti-staphylococcal Penicillins

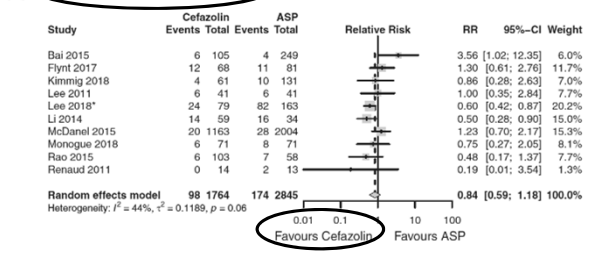
(b) 30-day all-cause mortality



Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins

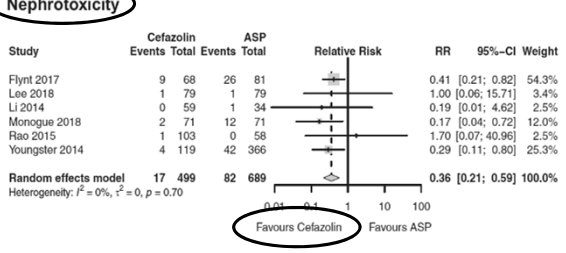
(c) Treatment failure / relapse



Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins

(d) Nephrotoxicity



Clinical Microbiology and Infection 25 (2019):818e827

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

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

- Anti-staphylococcal penicillins are not available in Argentina
- Cefazolin is the primary beta-lactam used to treat MSSA
- 54.5% prevalence (42/77 patients with SAB)
  - 7-day mortality CIE pos vs CIE neg: 12% vs 6% (p=0.44)
  - 30-day mortality CIE pos vs CIE neg: 40% vs 15% (p=0.03)

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

AHA Guidelines for S. aureus Native Valve Endocarditis

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

Circulation. 2015 Oct 13;132(15):1435-86

What about Ceftriaxone for MSSA Bacteremia?

- Meta-analysis of 12 retrospective cohort studies comparing ceftriaxone (n=1037) to SOC (n=2088)
- No significant difference in
  - Clinical cure rates
  - Microbiological cure rates
  - 30-day or 90-day mortality
  - 90-day readmission
  - Adverse drug reactions
- Caveats: patients in SOC were sicker, had more severe disease, endovascular infections, doses not well defined

Antibiotics 2022, 11:375

Summary: MSSA bacteremia

- Prefer a beta-lactam
- ASPs first drug of choice, but Cefazolin is better tolerated than ASPs
  - AHA second-line agent for native valve endocarditis
  - Overall mortality no worse, may be better compared to ASPs
  - Clinical failure rates and recurrences similar
  - Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients
- Avoid vancomycin, daptomycin if you must (ref below**)
- Ceftriaxone may be efficacious in selected patients, avoid for endocarditis, probably not a good answer on the boards

**Intern J Antimicrobial Agents 2021; 58:106363

Treatment of MRSA Bacteremia

2022 PREVIEW QUESTION

Q5. A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

Which one of the following would you recommend?

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

First-line choices for MRSA bacteremia

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

Holland et al: JAMA 312:1330, 2014

FDA-approved antibiotics for MRSA Infections

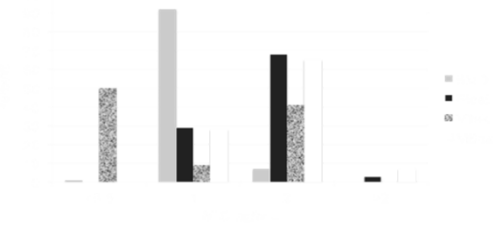
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr $\leq$ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic
Ceftaroline	SSTI, CAP	Rash, usual cephalopsorin reactions

FDA-approved antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Tedizolid	SSTI	May be less toxic than linezolid
Dalbavancin	SSTI	Single dose or 2 doses a week apart Lipoglycopeptide, related to teicoplanin
Oritavancin	SSTI	One time dose Lipoglycopeptide, related to vancomycin May artificially prolong PT, PTT

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

Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

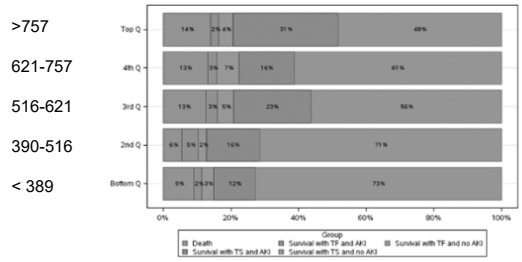
MIC is a Poor Predictor of Outcome

- Meta-analysis, 38 studies, 8291 episodes
- MIC < 1.5 µg/mL (low) versus MIC $\geq$ 1.5 µg/mL (high)
- Mortality low = 25.8%, high = 26.8%
- Adjusted risk difference = 1.6% (-2.3 to 5.6%), p = 0.43

Kalil, et al. JAMA 312:1552, 2014.

Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

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



Highlights of Modern Vancomycin Dosing for MRSA Infections

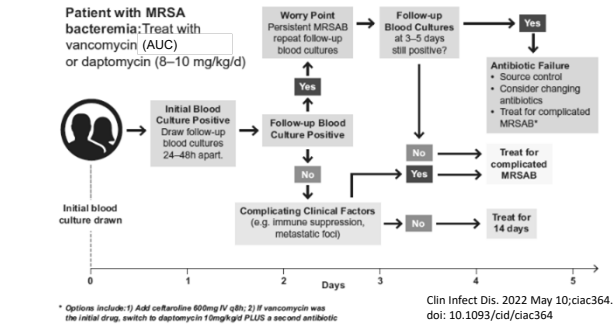
- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 mg*h/L(assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24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

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

AHA guidelines for therapy of native valve S. aureus endocarditis

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

Circulation. 2015 Oct 13;132(15):1435-86



Clin Infect Dis. 2022 May 10;ciac364. doi: 10.1093/cid/ciac364

Duration of Therapy for S. aureus BSI

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

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

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

Oral Therapy of S. aureus Bacteremia

- Quality of studies is low, subject to selection bias, confounding by indication
  - Relapse rates consistently higher with IV
  - Mortality rates consistently higher with IV
- Role in treatment of and efficacy for endocarditis, endovascular infections, complicated bacteremia not well defined
- May be an option for treatment of uncomplicated bacteremia in carefully selected patients, but there is a lack of standard definition
- ID consultation strongly recommended
- Prefer agents with good oral bioavailability: linezolid, T/S, FQ+rif, clindamycin (?), anti-staphylococcal beta-lactam (?)

See Dagher, et al. Open Forum Infect Dis 2020 May 5;7(6):ofaa151.

Combination Therapy of S. aureus BSI

Q6. Which one of the following combinations have been shown to improve mortality of patients with S. aureus bacteremia or native valve endocarditis?

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

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	
Adjunctive rifampin	RCT	MRSA, MSSA	No benef	29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSS	toxic	Various
Adjunctive dapto	RCT		No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	A	↑↑ AKI, higher mortality	32044943
Dapto + ceftar	aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Da fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Consider for salvage therapy, not first line

Monotherapy versus combination therapy for *Staph. aureus* bacteremia

- No high quality RCT has demonstrated improved mortality with combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are mostly low quality, retrospective, subject to bias, and based on subjective outcomes (e.g., change in therapy) not mortality, recurrence, metastatic infections*
- Reserve for salvage therapy

Possible exception: Dapto + Fosfo vs Dapto, Pujol, et al. Clin Infect Dis 2021; 72:1517

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

- Single center, retrospective study, 146 patients, ≥72h of dapto + ceftaroline combo
  - Combo: 66 on combo ≥ 10 days (IQR 13-21 days)
  - Mono: 74 on combo < 10 days (IQR 4-6 days)
    - De-escalated to dapto (n=30), ceftaroline (n=18), or vanco (n=26)
- Days of therapy prior to dapto + ceftaroline
  - Combo: 6 (IQR 4-9)
  - Mono: 7 (IQR 5-11)

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

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

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

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

Thanks

Back-Up Slides

Duration of Therapy of *S. aureus* Bacteremia

Duration of Therapy for S. aureus BSI

14 days	• UNCOMPLICATED • Fever resolves by day 3 • Sterile blood culture after 2-3 days (DOCUMENT!) • Easily removed focus of infection (no DVT) • No metastatic infection (e.g., osteo) • Negative echo, no evidence of endocarditis • No predisposing valvular abnormalities • (No implanted prosthetic devices, no DM, no immunosuppression)
4-6 weeks +	• COMPLICATED • Failure to meet one or more of above criteria • Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

How common is uncomplicated *S. aureus* Bacteremia?

Study	# eligible	# screened
Taupin	64 (10.4%)	612
14 day Rx	21	
>14 day Rx	43	
Holland (RCT)	116 (1.9%)	~6000*
Uncomplicated SAB	79	
Complicated SAB	37	

*Known or suspected complicated SAB at screening was an exclusion

Outcomes of Uncomplicated S. aureus Bacteremia: 14 days vs. >14 days

Outcomes	14 day Rx (n=21)	> 14 days Rx (n=43)
Death due to SAB	0	0
Relapse	0	2 (5%)
All cause mortality	2 (10%)	2 (5%)
Catheter-associated AE	0	7 (16%)
Adverse drug event	5 (24%)	7 (16%)

Taupin, OFID. 2020; 2020 Sep 29;7(10):ofaa457. doi: 10.1093/ofid/ofaa457

Duration of Therapy (DOT) and Outcome of SAB

- Retrospective cohort study, single center
  - 530 patients: 305 complicated, 225 uncomplicated
  - 17.7% MRSA
- Compared two DOT "breakpoints"
  - ≤ 14 days v > 14 days
  - ≤ 21 days v > 21 days
- Key results
  - Relapse rates: 4.0 % vs 3.8% and 3.1% vs 3.6%, respectively
  - Mortality: 29.3% v 15.8% and 20.8% v 11.1%
  - DOT > 14 day associated with lower mortality for complicated bacteremia but not uncomplicated bacteremia
  - DOT > 21 days not associated with lower mortality for either type of bacteremia (but unadjusted HR 0.46 [0.23-0.93] for complicated)

Abbas, et al. Clin Microbiol Infect 2020; 26:626,
See also review by Eichenberger, et al. Clin Microbiol Infect. 2020 May ; 26(5): 536–538

Even Shorter Course Therapy For Low Risk SAB?

- Retrospective study of 1005 patients from 3 cohorts of patients with "low risk" MSSA bacteremia
- 6-10 days of short-course (SC) treatment vs 11-16 days, prolonged course (PC)
- PC patients had higher CRPs, more HA infections, more ECHOs, more PO therapy

Cohort (N)	Mortality		Relapse	
	SC	PC	SC	PC
I (645)	19.3%	19%	5.4%	8.4%
II (219)	23%	20.7%	--	--
III (141)	17.6%	20%	--	--

Thorlacius-Ussig, et al. 2021; Clin Infect Dis 73:866

Oral Therapy of S. aureus Bacteremia

Recent Studies of Oral Therapy - 1

PMID	Study Design	SAB Populaiton	Oral Agents	Median Duration	Relapse/ Clinical Failure	Mortality
33606007 CID 2021	Retrospective cohort Single center	Comp 96% MSSA No endovascular infection, neg PET-CT, neg ECHO 45 IV 61 PO Switch	Clindamycin	IV: 45 days PO: 44 days	IV: 0 PO: 0	IV: 13.3% PO: 7%
33157291 IJID 2021	Retrospective cohort Single center	Comp (n=75) Uncomp (n=126) 18% MRSA 76 IV 125 PO Switch	T/S (66%) FQ (18%) Linezolid (9%)	IV: 22 days PO: 25 days	IV: 6% PO: 3%	IV: 16% PO: 7%

Recent Studies of Oral Therapy - 2

PMID	Study Design	SAB Populaiton	Oral Agents	Median Duration	Relapse/ Clinical Failure	Mortality
32015029 AAC 2020	Retrospective cohort Single center	Uncomplicated 95% MSSA 16 IV 84 PO	Fluclox: 71% Cephalexin: 8% T/S, Clinda: 10%	IV: 16 d PO: 14 d	IV: 6% PO: 4%	IV: 6% PO: 2%
30418557 JAC 2019	Retrospective cohort Single center	Comp (n=320) Uncomp (n=172) 100% MRSA 422 IV 70 PO Switch	Linezolid (50%) T/S (34%) Clinda (11%)	IV: 35 d PO: 21 d	IV: 14.9% PO: 7.1%	IV: 5.5% PO: 1.4%
30351401 CID 2019	Prospective cohort Single center	Low Risk 16% MRSA 107 IV 45 PO	Linezolid	IV: 15 d PO: 15 d	IV: 3.7% PO: 2.2%	IV: 15.9% PO: 2.2%

De-Escalation of Combo Therapy

263 patients, NVE, osteo, brain abscess (1), ≥4 d MRSA + BC

↓

80 patients, vanco/dapto + ceftaroline

↓

30 evaluable patients
15 combo
15 mono

Outcome	Mono	Combo
AKI	6	7
Leukopenia	0	1
Recurrence	1	0
Readmission	2	0
Death	1	3

Infect Dis Ther (2020) 9:77–87

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

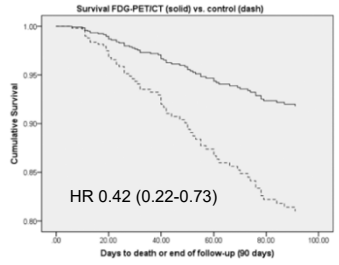
Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia

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

Clinically suspected sites (n=136)		PET/CT + sites (n=179)	
PET/CT +, confirmed	72 (53%)	PET/CT +, clinically unsuspected	145 (69%)
PET/CT -, excluded	64 (47%)	PET/CT +, clinically suspected	72 (31%)

Clin Infect Dis. 2021;73:e3859

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



Issues:
--Availability
--Reimbursement
--Observation studies only

Clin Infect Dis. 2021;73:e3859

22

Helicobacter and Clostridioides Difficile

Dr. David Aronoff

22 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Helicobacter and Clostridioides difficile

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

6/12/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

HELICOBACTER PYLORI

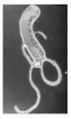
Some good references:

Crowe SE. *N Engl J Med* 2019;380:1158-65
Cho H, *et al. Gastroenterol Clin N Am* 2021; 50: 261-282
Ansari S and Yamaoka Y. *Clin Micro Rev* 2022 *in press*
Lee Y, *et al. Annual Rev Med* 2022; 73: 183-95

Microbiology: *Helicobacter pylori*

Gastric Mucosa

- Spiral-shaped
- Flagellated
- Non-invasive



First isolated in 1983
Nobel Prize (Marshall & Warren, 2005)
NEJM 362: 1597, 2010

Agar

- Slow-growing (3-7 days)
- Gram negative rod
- Microaerophilic (5% O_2)
  - Catalase +
  - Oxidase +
  - Urease + → Survival

$Urea \rightarrow CO_2 + NH_3 \rightarrow \uparrow pH$ Colonization
Diagnostic testing

Question #1

A young woman undergoes upper endoscopy for unexplained nausea & vomiting. The stomach appears normal. Surveillance biopsies are taken & the gastric biopsy urease test is positive. The biopsies are most likely to show:

A. Hp organisms, but no gastric or esophageal inflammation.
B. Hp organisms plus gastric inflammation (gastritis).
C. Hp organisms plus esophagitis.
D. Neither Hp organisms, nor inflammation because the urease test is often false positive with a normal endoscopy.

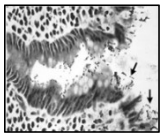
Question #2

What is the most likely source for humans to acquire *H. pylori* infection?

A. Perinatally from mother
B. Ingestion of raw vegetables
C. Ingestion of undercooked meat
D. Ingested tap water from a municipal source
E. Contact with infected secretions from another human

Helicobacter pylori: Key Points

- Humans are the only natural Hp host
- Infects > 50% of the world's population
  - US ~20-40%*
- A leading chronic infection in humans
  - Similar to dental caries
- 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: Key Points

Hp causes an inflammation-driven cancer

Chronic active gastritis
↓
Atrophic gastritis
↓
Epithelial metaplasia
↓
Intraepithelial neoplasia
↓
Invasive carcinoma

Lee Y, *et al. Annu Rev Med* (2022)

Transmission of *H. pylori*

- Exact route of transmission is not known
- Likely fecal-oral or oral-oral
- Intrafamilial spread – (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)

Disease Paths for *Helicobacter pylori* Infection

• Asymptomatic gastritis	85-90%
• Peptic ulcer (DU, GU)	1-17%
• Gastric cancer	0.1-3%
• MALT lymphoma	<0.01%

DU, duodenal ulcer
GU, gastric ulcer
MALT, mucosal-associated lymphoid tissue

Lee Y, *et al. Annu Rev Med* (2022)
NEJM 347: 1175, 2002
Gut 66:6, 2017

H. pylori: Disease Associations

- #1 cause of chronic gastritis
- PUD: 90% of DU, 80% of GU
- MALT lymphomas (72 – 98%)
- Gastric Cancer (60 – 90%)*

} Hp causal

H. pylori is a World Health Organization-designated carcinogen & the strongest known risk factor for non-cardia gastric

- Iron deficiency anemia, B12 deficiency, ITP
- Eradication Hp neither causes nor exacerbates GERD
- Hp poss. reduces risk for Barrett's esophagus/esophageal CA

HP is classified by WHO as a Class 1 carcinogen.
MALT = mucosal-associated lymphoid tissue

Maastricht V. Gut 66:6, 2017
Kasahun GG, Infect Drug Resist 13:1567-1573, 20
Shah SG, et al. Gastroenterology 2021;160:1831

Question #3

2022 PREVIEW QUESTION

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

The best approach to the diagnosis of *H. pylori* infection in this patient is:

A. Immediate Hp serology
B. Immediate Hp stool antigen EIA
C. Endoscopy with rapid urease test (RUT)
D. Immediate ^{13}C Urea Breath Test
E. D/C PPI for 2 weeks then Hp stool antigen EIA

Who Should Be Tested for Hp?

Patients with:

- **Suspected Hp infection (e.g., active DU)**
- **Current or past GU or DU**
- **Uninvestigated dyspepsia**
- **Gastric mucosa-associated lymphoid tissue lymphoma**
- **Family members in same household of pt w/ proven, active Hp infection**
- **Family hx of PUD or gastric cancer**
- **1st generation immigrants from high-prevalence areas**
- **High-risk groups (Latino, Black/AA, indigenous populations)**
- **Regular user of NSAIDs**
- **Long-term PPI use**
- **Fe deficiency anemia (unexplained)**
- **ITP (low evidence base)**

Lee Y, *et al. Annu Rev Med* (2022)

Diagnosis of *H. pylori Infection*

Noninvasive (global)	Sensitivity	Specificity	
Urea Breath Test UBT (^{13}C)	> 90 – 95%	> 90 – 95%	Live Hp
Stool Antigen (monoclonal)	> 90 – 95%	> 90 – 95%	Live & dead Hp
Serology	85%	79%	Detects exposure

NO:

Biopsy-based (sampling error)	Sensitivity	Specificity	
Rapid urease test	90%	95%	2-5 bx recommended
Histology	90 – 95%	95 – 98%	
Culture	73%	100%	Difficult

Serology is not useful. UBT considered 'best test'. Antigen test is usually less expensive.
Use only monoclonal stool Ag tests.
Histology requires 10^4 organisms to visualize

Lee Y, *et al. Annu Rev Med* (2022)

Testing Limitations for Hp

PPI
Antibiotics
Bismuth
Bleeding

Interfere with all Hp tests because they reduce bacterial load

False negatives due to decreased Hp burden
Recommend delay diagnostic testing until:

- **PPI stopped for > 2 weeks** (OTC antacids & H2RA do <u>not</u> affect UBT/SA testing)
- **Antibiotics, bismuth stopped for > 4 weeks**
- **Bleeding stopped for 4-8 weeks**

Lee Y, et al. Annu Rev Med (2022)
Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Initial Diagnosis of *H. pylori* with Dyspepsia

MOST = NONINVASIVE

- **Stool antigen test (SAT)**
- **Urea Breath Test (UBT)**

- **Endoscopy mandatory if ≥60 years old or 'alarm symptoms or signs':**
  - **Unexplained iron-def anemia**
  - **GI bleeding**
  - **Unintentional weight Loss**
  - **Palpable mass**
  - **Severe abdominal pain**
  - **Persistent vomiting**
  - **Progressive dysphagia / odynophagia**

Crowe SE, UpToDate (2018)
Crowe SE, NEJM 380:1158-65 (2019)

Question #4

2022 PREVIEW QUESTION

- **Which of the following is the most appropriate next step for evaluating a 29-year-old previously healthy but overweight male patient with typical retrosternal heartburn symptoms?**
  - **A. Stool antigen test for *H. pylori***
  - **B. Urea breath test for *H. pylori***
  - **C. No testing for *H. pylori***
  - **D. Serological testing for *H. pylori***
  - **E. Empiric therapy for *H. pylori* regardless of testing**

Explanation for Q#4

- ***H. pylori* is not implicated as an etiological factor in gastroesophageal reflux disease (GERD)**
- **Treatment for (eradication of *H. pylori*) can increase the risk for Barrett's esophagus and esophageal adenocarcinoma**
- **Serology is not a recommended test for *H. pylori***

Siddique O, *et al. AJM* 2018

Question #5

A 23 yo woman presents with persistent epigastric discomfort diagnosed as Hp+ gastritis by endoscopy. Fecal Hp antigen is also positive. Last year she was treated with azithromycin for a respiratory tract infection. As a child, she was treated repeatedly with PCN/amoxicillin for recurrent tonsillitis.

What do you recommend for therapy?

A. **Clarithromycin + amoxicillin + PPI**
B. **Metronidazole + erythromycin + PPI**
C. **Bismuth subsalicylate + TCN + metronidazole + PPI**
D. **Metronidazole + amoxicillin + PPI**
E. **PPI therapy alone given her age**

Who should be treated for *H. pylori* infection?

Houston Consensus Conference on Testing for *Helicobacter pylori* Infection in the United States

Hashem B. El-Serag,[1,7] John Y. Kao,[2] Fasiha Kanwal,[1,7,11] Mark Gilger,[3,4] Frank LoVecchio,[5] Steven F. Moss,[22] Sheila Crowe,[23] Adam Elfant,[11] Thomas Haas,[11] Ronald J. Hapke,[24] and David Y. Graham[25]

- **"We recommend that all patients with active *H pylori* infection be treated"**
- **"Infection causes chronic progressive damage to the gastric mucosa that in 20%–25% of individuals will result in life-threatening clinical outcomes such as peptic ulcer or gastric cancer"**

El-Sarag HB, *et al. Clin Gastroenterol Hepatol 2018;16:992-1002*

Takeaways about Treatment of Hp

- **Cure rates of most Hp therapies are relatively low (e.g., 80% or lower).**
- **Antibiotic resistance is a HUGE challenge, even with 3-drug therapies, provoking newer quadruple therapies**
- **Ask about prior antibiotic exposure hx (clarithromycin/metronidazole/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**
  - **Acidity hinders stability & activity of macrolides, amoxicillin**

Lee YC, Annu Rev Med (2022)

Takeaways about Treatment of Hp

- **Combination drug therapy is essential**
- **The optimal duration of Hp therapy is 14 days**
- **Therapies should be susceptibility-based, relying either on susceptibility testing or on proven high local success rates**
  - **Consider abx resistance patterns & testing**
  - **Culture-based and non-culture-based (NGS) techniques can determine resistance**
- **Success should always be confirmed by a test of cure after treatment of every patient (*e.g.*, UBT performed 4 or more weeks after therapy)**

Lee YC, Annu Rev Med (2022)

Eradication of *Helicobacter pylori*

- **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

RIFABUTIN-Based Combinations

- **2020: The FDA approved fixed-dose combination of omeprazole, amoxicillin & rifabutin (Talicia) for *Hp* treatment in adults**
- **Omeprazole 10 mg, amoxicillin 250 mg, & rifabutin 12.5 mg**
  - **The recommended dosage is 4 capsules (with food) every 8 hours for 14 days.**

Summary: Omeprazole/Amoxicillin/Rifabutin (*Talicia*)

- A fixed-dose, rifabutin-based, 3-drug combination FDA-approved for treatment of *Helicobacter pylori* infection.
- First rifabutin-based product to be approved for treatment of *H. pylori* infection.
- Rifabutin-based triple therapy has been used for years as a salvage regimen for treatment-refractory *H. pylori* infection.
- Approval was based on the results of two trials in treatment-naive patients; *H. pylori* was eradicated in about 80% of those treated with the combination.
- How the efficacy of *Talicia* compares to that of other regimens used for first-line treatment of *H. pylori* infection is unknown.
- Rates of *H. pylori* resistance to rifabutin have been low; whether more widespread use as part of a first-line regimen would result in higher rates of resistance remains to be established.
- Common adverse effects include diarrhea, headache, rash, and dyspepsia.
- Has the potential to interact with many other drugs.

The Medical Letter (2020)

Eradication of *Helicobacter pylori*

- Fluoroquinolone resistance is common now (>50%)
  - They are not recommended in 1st-line treatment regimens
- Resistance to amoxicillin, tetracycline & rifabutin is uncommon
- Clinical significance of resistance to metronidazole not straightforward

Shah SC, *et al. Gastroenterology* 2021;160:1831-1841
Cho J, *et al. Gastroenterol Clin N Am* 50 (2021) 261-282
Hulten KG, *et al. Gastroenterology* 2021

Question #6

After treatment of this patient for Hp gastritis, the *H. pylori* stool antigen test should be repeated:

A. On the final day of *H. pylori* therapy
B. Two weeks after completion of *H. pylori* therapy
C. Four weeks after completion of *H. pylori* therapy
D. The test should not be repeated to assess cure

Management Issue:
Test of cure for *H. pylori* Infection

- Stool antigen test Perform ≥ 4 weeks post-Rx
- Urea Breath Test Perform ≥ 4 weeks post-Rx

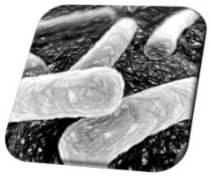
Some recommend testing 6-8 weeks post-Rx

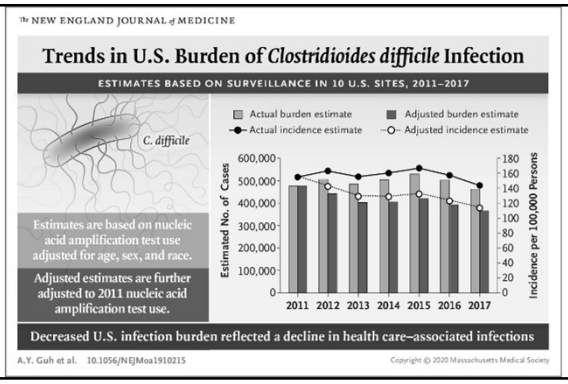
Endoscopy required if gastric ulcer, for example

Maastricht V. Gut 66:6, 2017

DA4

CLOSTRIDIOIDES DIFFICILE



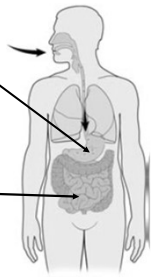


Antibiotic-associated Diarrhea (AAD)

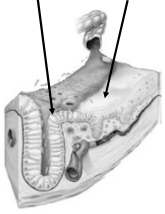
- Common
  - In 5-25% of antibiotic treatment courses especially with > 3 days of Abx but one dose is sufficient
- 10-40% of AAD is associated with *C. difficile* infection (CDI) but nearly all AA colitis is CDI
- Disruption of colon microbiome & bile acid physiology are key mechanisms

Pathogenesis of CDI

1. CDI spores survive in the environment for long periods of time. Following ingestion, they traverse the acidic environment of the stomach.
2. Spores germinate within the intestine.



3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.
4. Toxin A & B production leads to colon damage +/- pseudomembrane.



Slide adapted from CDC.gov. Sunenshine & McDonald Cleve Clin J Med 2006; 73(2):187-197.

Common Clinical Manifestations

- Watery & mucusy diarrhea up to 10 - 15 times daily
- Lower abdominal pain & cramping
- Low grade fever (15%+)
- Leukocytosis (> 15,000 cells/ml = severe)
- Nausea
- Anorexia
- Malaise

http://year9diseases.wikispaces.com/

Complications of CDI

- Sepsis ± multiple organ dysfunction
- Megacolon: need for surgical interventio
  - Colectomy
  - Loop iliostomy
- Bowel Perforation
- Lack of treatment response
- Recurrent infection (20%+)
  - Relapse
  - Reinfection

Major Risk Factors for Acquisition of CDI

1. Antibiotic use
   - Disruption of microbiome
2. Recent hospitalization or LTCF
   - Increased exposure
   - Co-morbidities reduce immunity or alter microbiome
3. Age > 65 years
   - Reduced gastric acidity
   - Impaired immunity
   - Altered microbiome

REMEMBER:
Even healthy people in the community without antibiotic exposure can get CDI

Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48
Loo V, *et al. NEJM*. 365;18

Minor Risk Factors for Acquisition of CDI

4. Gastric acid suppression (proton pump inhibitor)
   - Reduced biochemical defense
   - Altered microbiome
5. Abdominal surgeries
   - Altered microbiome
6. Immunocompromised host
   - Impaired mucosal immunity
   - Altered microbiome

McFarland LV. *Curr Opin Gastroenterol*. 2009 Jan;25(1):24-35
Dubberke E, *et al. Infect Control Hosp Epidemiol* 2011;32(4):360-366
Pacheco & Johnson. *Curr Opin Gastroenterol* 2013, 29:42-48

CDI Severity

- Leukocytosis
- AKI
- Sepsis/shock
- Megacolon

Stool frequency is not part of severity assessment

Clinical Definition	Supportive Clinical Data
Nonsevere	Leukocytosis with a WBC count of ≤15,000 cells/mL and a serum creatinine level <1.5 mg/dL
Severe	Leukocytosis with a WBC count of ≥15,000 cells/mL or a serum creatinine level >1.5 mg/dL
Fulminant	Hypotension or shock, ileus, megacolon

Table from Wilcox M, *IDSE* (2018)
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

Speaker: David Aronoff, MD

C. difficile Diagnostic Testing

Whom to test?

- Appropriate epidemiology/ill with diarrhea/endoscopic findings
  - No laxatives within last 48 hrs
- Test diarrheal stools (unless ileus). *One stool.*
  - >3 liquid stools over 24h
- Only test specimens if patient > 1 year old

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994

C. difficile Diagnostic Testing

Simplified approach:

Diarrhea* + Toxigenic *C. difficile* &/or toxin in stool → TREAT

*No laxatives or other obvious causes

C. difficile Diagnostic Testing

Nucleic acid amplification test (NAAT; PCR):

Detects the gene for toxin B

Advantages	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• Does not detect actual toxin • Can't differentiate colonization *vs* infection

Patient selection is critical

C. difficile Diagnostic Testing

Glutamate dehydrogenase (GDH) antigen EIA:

Detects *C. difficile* bacteria by secreted antigen

Advantages	Disadvantages
• High sensitivity • Rapid • Relatively inexpensive	• Does not detect toxin • Detects NON-toxigenic strains • Cannot differentiate colonization from infection

Must be combined to test for toxin (NAAT or EIA)

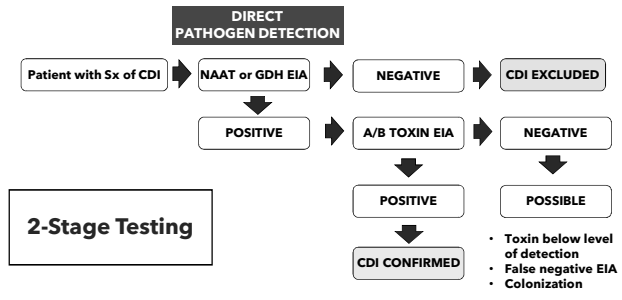
C. difficile Diagnostic Testing

Toxin A/B detection by EIA:

Detects *C. difficile* toxin(s) directly

Advantages	Disadvantages
• Good specificity • Rapid • Relatively inexpensive	• Poor sensitivity • False positives possible

Usually used in a 2-step protocol with NAAT or GDH



Czepiel J, et al. Eur J Clin Micro Infect Dis (2019)

CDI TAKE AWAYS

Careful selection of patients for testing, especially with NAATs, is extremely important

Only patients with diarrhea (≥3 stools in ≤24 hrs)

NO formed or soft stools (unless ileus)

NO 'Test of Cure'

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. **Vancomycin 125 mg PO qid x 10 days**
  d. **Bezlotoxumab + vancomycin x 10 days**
  e. **Fidaxomicin 200 mg PO BID + metronidazole 500 mg PO TID x 10 days**

Therapy of CDI

- **D/C antibiotics/change to 'lower risk abx'**
- **Avoid antiperistaltics**
- **Recurrent CDI occurs in ≥1 in 5 patients**

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1-24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650-668

Therapy of CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	**VANCOMYCIN 125 mg po QID x 10 d** **FIDAXOMICIN 200 mg po BID x 10 d**
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.

No more metronidazole
(unless mild disease, in young person, +/- cost constraints)

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1-24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650-668

Recurrent CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation[c]

McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1-24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650-668

Recurrent CDI

- **Bezlotoxumab, a monoclonal antibody directed against toxin B produced by C. difficile, has been approved as adjunctive therapy for patients who are receiving antibiotic treatment for CDI & who are at high risk for recurrence**
- **≥65 years old with >1 additional risk factor:**
  - **Experiencing 2nd episode of CDI within 6 mo**
  - **Immunocompromised, or severe CDI**

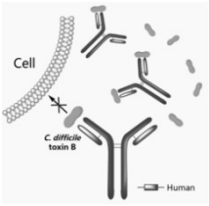


Figure from http://en.pharmacodia.com/web/drug/1_9806.html
McDonald LC, *et al. Clin Infect Dis.* 2018 Mar 19;66(7):987-994
Kelly CR, *et al. Am J Gastroenterol* 2021;00:1-24
Poylin V, *et al. Dis Colon Rectum* 2021; 64: 650-668

22 – Helicobacter and Clostridium Difficile

Speaker: David Aronoff, MD

Prevention of *C. difficile* Disease (HCW & visitors)

Contact precautions for patient care.

Gloves, gowns while diarrhea persists.

Single rooms

Handwashing with SOAP & WATER

Alcohol gel rubs do not kill *Cd* spores

Sporocidal solutions for hospital cleaning.

(eg. hypochlorite solutions)

Antibiotic restriction policies

(Antimicrobial stewardship programs).

Lancet ID 17:194, 2017 Scotland
Lancet ID 17:411, 2017 England

CDI TAKE AWAYS

Epidemiology

- **Most CDI is health-care associated**

Diagnosis

- **Need to demonstrate toxin B in stool with NAATs, EIA**
- **Send only unformed stools when diarrhea meets CDC definition**

Treatment: Primary or Recurrent CDI

- **Vancomycin & fidaxomicin > metronidazole**
- **Bezlotoxumab & fidaxomicin associated with lower risk for recurrent CDI**
- **Consider FMT for second or more recurrence**

Prevention

- **Hand wash as alcohol gels ineffective**
- **Bleach**
- **Antimicrobial Stewardship Programs**

New Guidelines 2021


Clinical Infectious Diseases
IDSA GUIDELINES

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults

Clinical Infectious Diseases 2021

23

Hospital Epidemiology

Dr. Michael Klompas

23 – Hospital Epidemiology
Speaker: Michael Klompas, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Hospital Epidemiology

Michael Klompas MD, MPH, FIDSA, FSHEA
Professor, Harvard Medical School
Hospital Epidemiologist, Brigham and Women's Hospital

7/18/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Grant funding:
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
  - Mass Department of Public Health
- Royalties
  - UpToDate

Topics

- **Fomites:** do hand hygiene and contact precautions work?
- **Air:** respiratory pathogen transmission & prevention
- **Water:** the source of all evil
- ***Clostridioides difficile*:** you are your own enemy
- **Devices:** the other source of all evil
- **Cluster investigation:** find the missing link

Question #1

What is the most common healthcare-associated infection?

A. Central line associated bloodstream infections
B. Catheter-associated urinary tract infections
C. Hospital-acquired pneumonia
D. Surgical site infections
E. *Clostridioides difficile*

The Most Common Hospital Acquired Infections

CDC point-prevalence survey of healthcare-associated infections in 2015, 199 hospitals, 10 states

	Frequency per 100 patients
Pneumonia	0.9
Surgical site infections	0.7
Gastrointestinal infections including *C. difficile*	0.6
Bloodstream infections	0.4
Urinary tract infections	0.3
Any healthcare-associated infection	3.2

Magill, *N Engl J Med* 2018;379:1732-1744

Question #2

What is the most common healthcare-associated pathogen?

A. *Pseudomonas aeruginosa*
B. *Staphylococcus aureus*
C. *Klebsiella pneumoniae*
D. *Candida albicans*
E. *Clostridioides difficile*

The Most Common Hospital Acquired Pathogens

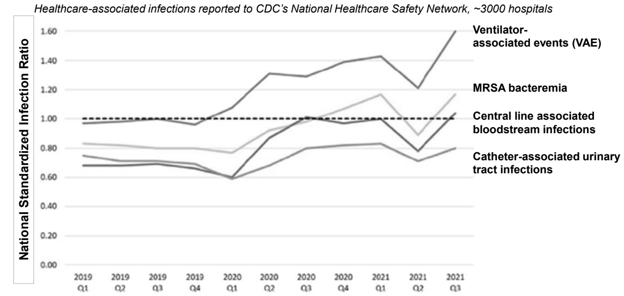
CDC point-prevalence survey of healthcare-associated infections in 2015, 199 hospitals, 10 states

	Frequency per 100 healthcare-associated infections
C. difficile	15%
Staphylococcus aureus	11%
Escherichia coli	10%
Candida species	6%
Enterococcus species	5%
Enterobacter species	5%
Pseudomonas aeruginosa	5%
Klebsiella species	5%

Magill, *N Engl J Med* 2018;379:1732-1744

Impact of the pandemic on U.S. HAI rates

Healthcare-associated infections reported to CDC's National Healthcare Safety Network, ~3000 hospitals



Lastinger, *Infection Control & Hospital Epidemiology* 2022;ePub ahead of print

Question #3

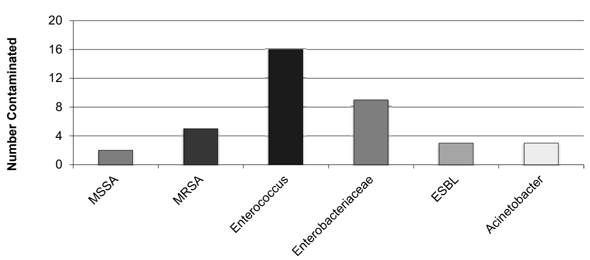
Your hospital's Chief Quality Officer is exasperated that hand hygiene compliance rates in your hospital continue to hover around 60-70% despite years of trying to improve performance. What evidence-based strategies can you recommend to improve compliance?

A. Improve data collection by deploying more secret observers
B. Do an educational blitz on the benefits of hand hygiene
C. Give high performing staff gift cards
D. Create an accountability model wherein failure to conduct hand hygiene will be managed like other serious performance lapses

How can we improve hand hygiene rates and will it make a difference?

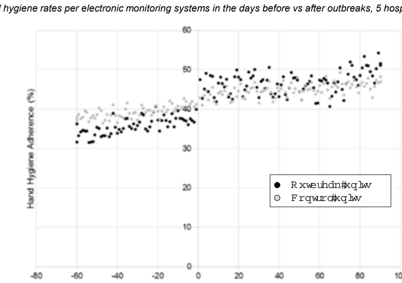
Organisms Recovered from Physicians' Hands Following a Single Physical Exam

Standardized exams of 56 patients, hand hygiene & sterile gloves prior to exam



Association between Hand Hygiene Rates and Outbreaks

Analysis of hand hygiene rates per electronic monitoring systems in the days before vs after outbreaks, 5 hospitals, 26 inpatient units



Kovacs-Litman, *Clin Infect Dis* 2021;73:e3656-60

How do we improve hand hygiene?

OPEN ACCESS

Comparative efficacy of interventions to promote hand hygiene in hospital: systematic review and network meta-analysis

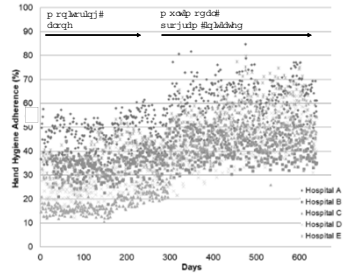
Nantasit Luangasanatip,[1,2] Maliwan Hongsuwan,[1] Direk Limmathurotsakul,[1,3] Yoel Lubell,[1,4] Andie S Lee,[5,6] Stephan Harbarth,[5] Nicholas P J Day,[1,4] Nicholas Graves,[2,7] Ben S Cooper[1,4]

Core Model	Provide infrastructure
	Education and training
	Feedback
	Reminders
	Institutional safety culture
Plus	Goal setting
	Reward incentives
	Accountability

Luangasanatip *BMJ* 2015;351:h3728

Hand Hygiene Rates per Electronic Monitoring Systems

Assessment of hand hygiene rates following installation electronic monitoring + multimodal QI program, 5 hospitals, Toronto



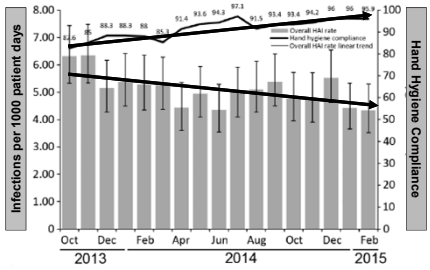
Electronic monitoring alone insufficient. Need a multimodal program for success.

1. Engage HCPs to specify hand hygiene dispenser locations
2. Educate each unit about electronic monitoring and share baseline rates
3. Provide weekly reports to unit managers and staff on hand hygiene performance
4. Post visual reminders about the importance of hand hygiene
5. Create a safety climate

Leis, *Clin Infect Dis* 2020;71:e680-685

All Hands on Deck!

Better Hand Hygiene, Fewer Healthcare Associated Infections



Sickbert-Bennett, Emerg *Infect Dis* 2016;9:1628-1630

Question #4

You are sick and tired of having to put on gloves and gown every time you enter the room of a patient with a history of MRSA. You wonder: do contact precautions actually prevent infections?

A. Contact precautions do little to prevent the spread of resistant bacteria
B. Contact precautions prevent healthcare-associated infections
C. The impact of contact precautions on infections with resistant bacteria remain unclear – need more longterm data
D. Contact precautions will prevent infections but are associated with significant increased risk of psychological harm to patients
E. Contact precautions prevent infections but only in surgical patients

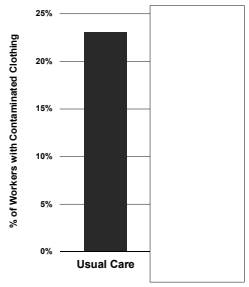
VIEWPOINT

Contact Precautions for Endemic MRSA and VRE
Time to Retire Legal Mandates

VIEWPOINT

The Importance of Contact Precautions for Endemic Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant Enterococci

Clothing Contamination



- **Most common pathogens:**
  - ***Staph aureus***
  - ***Enterococcus sp.***
  - *Stenotrophomonas*
  - *Pseudomonas*
  - *Acinetobacter*
  - *Enterobacter*
  - *Klebsiella*

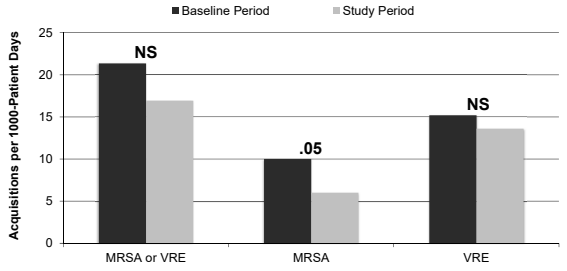
Contact Precautions

- **Expensive**
- **Onerous**
- **Diminish patient contact**
- **More non-infectious adverse events**
- **More depression and anxiety**
- **Lower patient satisfaction**

Am J Infection Control 2009;37:85-93

Universal vs Targeted Contact Precautions in ICUs

Cluster-randomized trial in 20 ICUs of gloves & gowns for all patients versus colonized patients alone



Harris, *JAMA 2013*;310:1571-80

Universal vs Targeted Contact Precautions

Cluster-randomized trial in 20 ICUs of gloves & gowns for all patient encounters versus usual care

- **Universal gloves and gowns also associated with:**
  - **Less healthcare worker entries into patients' rooms**
    - 4.3 vs 5.2 entries per hour, P=.02
  - **No difference in adverse events**
    - 59 vs 74 events per 1000 patient-days, P=.24
  - **Equivocal effect on hand hygiene**
    - No change in room entry compliance (56% vs 50%, P=.42)
    - Higher room exit compliance (78% vs 63%, P=.02)

Elimination of Routine Contact Precautions for Endemic Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus*: A Retrospective Quasi-Experimental Study

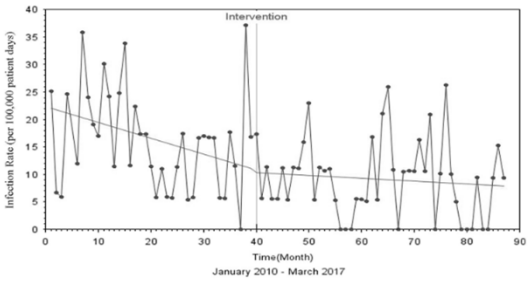
Evaluation of Vancomycin-Resistant Enterococci (VRE)–Associated Morbidity Following Relaxation of VRE Screening and Isolation Precautions in a Tertiary Care Hospital

Impact of Discontinuing Contact Precautions for Methicillin-Resistant *Staphylococcus aureus* and Vancomycin-Resistant *Enterococcus*: An Interrupted Time Series Analysis

Evaluation of contact precautions for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*

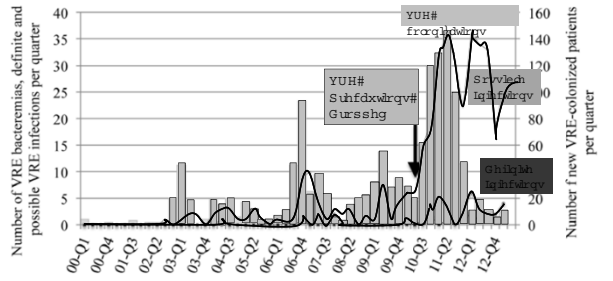
Discontinuing Contact Precautions for MRSA and VRE

Virginia Commonwealth University



Infection Control Hospital Epidemiol 2018;39:676-682

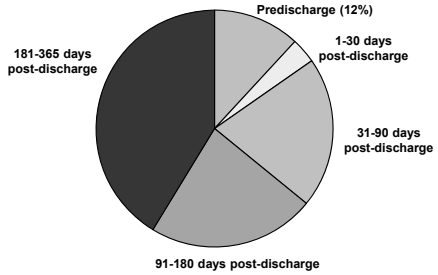
A Note of Caution



Popiel, *Infection Control Hospital Epidemiol* 2014;35:818-825

Most MRSA Infections Occur AFTER Discharge

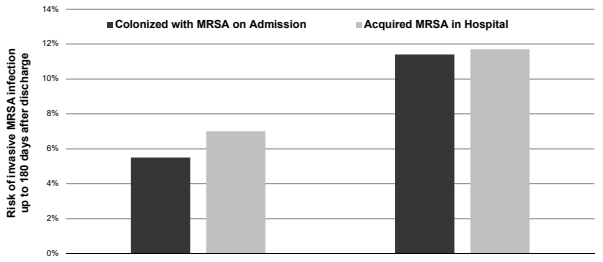
985,626 admissions to VA hospitals, 2008-2015



Nelson, *Clin Infect Dis* 2019;68:545-553

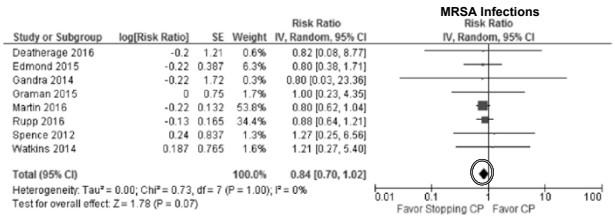
Risk of Invasive Infection Highest for Newly Colonized

Risk of invasive MRSA up to 180 days post-discharge amongst 985,626 admissions to VA hospitals, 2008-2015



Nelson, *Clin Infect Dis* 2019;68:545-553

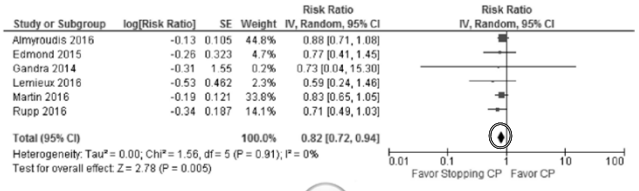
Impact of Discontinuing Contact Precautions on MRSA



Trend towards <u>fewer</u> MRSA infections after stopping contact precautions

Am J Infection Control 2018;46:333-340

Impact of Discontinuing Contact Precautions on VRE

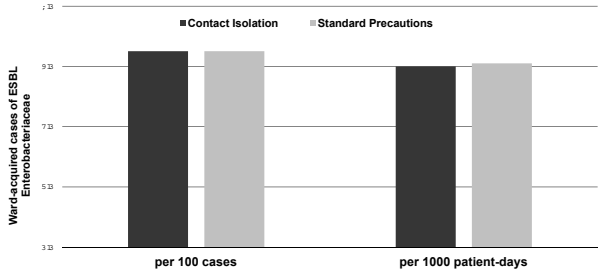


<u>Significantly</u> <u>fewer</u> VRE infections after stopping contact precautions

Am J Infection Control 2018;46:333-340

Contact Precautions for Resistant Gram Negatives

Cluster randomized trial, contact precautions vs standard precautions, 20 non-ICUs, 4 hospitals in Europe

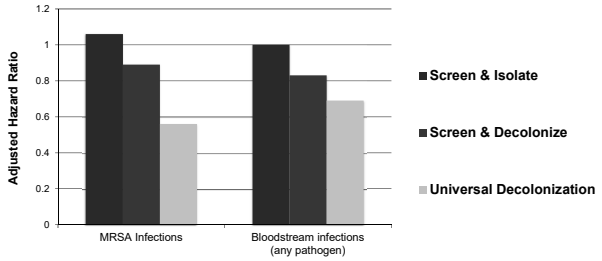


Limitations

- Most studies single center
- All studies observational
- Limited duration of follow up
- No active surveillance to detect silent transmission
  - Most studies track HAI rates rather than new colonization
- Low event rates and thus limited power
- Limited data on parallel interventions
  - Hand hygiene rates, chlorhexidine bathing, quality of environmental cleaning, etc.

Decolonizing patients may be better than isolating carriers

*Cluster randomized trial of **MRSA screen & isolate** vs **screen & decolonize** vs **decolonize everyone**, 74 ICUs, 43 hospitals*

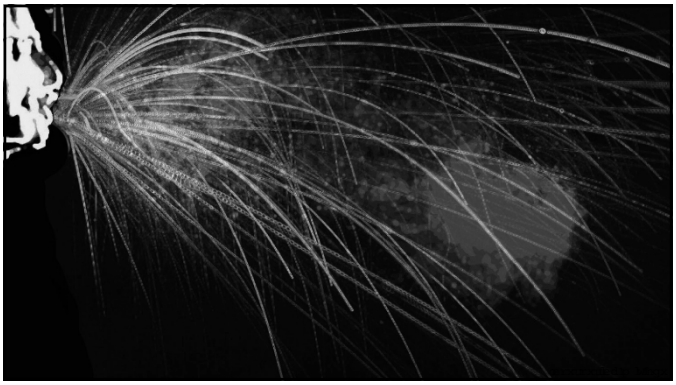


Huang et al. *NEJM* 2013:368:2255-65

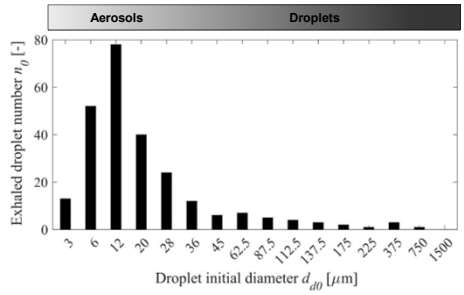
Question #5

Your vaccinated co-worker is convinced she caught SARS-CoV-2 at work despite adhering to the hospital's policy requiring all healthcare workers to wear a surgical mask for all patient encounters. She did care for a patient who was diagnosed with SARS-CoV-2 infection on hospital day 4 following an elective admission for breast surgery. Your boss asks if it is possible your co-worker was infected by this patient despite wearing a surgical mask?

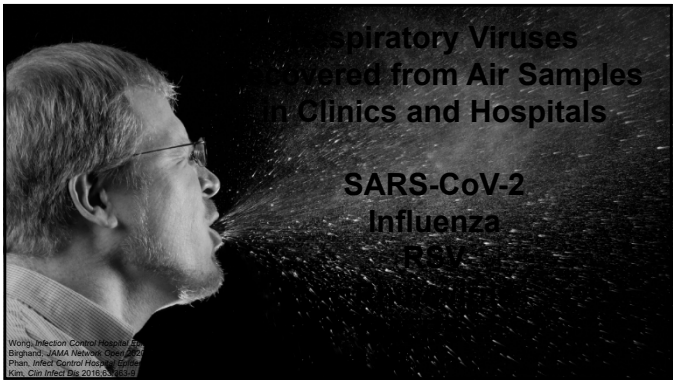
A. No, surgical masks provide excellent protection against respiratory viruses
B. No, breakthrough infections are very unusual in vaccinated people
C. No, SARS-CoV-2 in HCWs is almost always acquired outside the hospital
D. Yes, surgical masks provide partial protection against respiratory viruses
E. Yes, surgical masks do not provide any protection against respiratory viruses



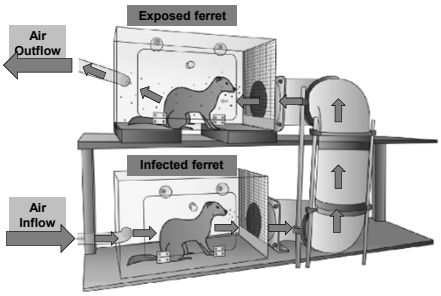
People Produce Respiratory Particles in a Range of Sizes



Chen. *Building and Environment* 2020;176:106859



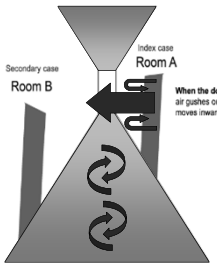
Transmission via Aerosols



- Ferret model used to assess aerosol transmission
- 4 uninfected ferrets exposed to ferrets infected with SARS-CoV-2 & influenza
- Airflow between cages via closed pipe, 1.1m long, 4 right-angle turns
- 2/4 ferrets exposed to SARS-CoV-2 infected
- 4/4 ferrets exposed to influenza infected

Kutter, *Nature Communications* 2021;12:1653

Aerosol Transmission in Humans: Quarantine Hotels



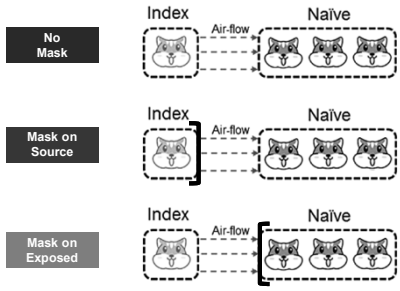
- Multiple case reports of transmission between unrelated travelers staying in quarantine hotels in Hong Kong, Singapore, New Zealand…
- Quarantine hotels have very strict rules in hotels requiring guests to stay in their own room at all times (video monitoring)
- Transmission presumed due to
  - Prolonged dwell time in poorly ventilated room leading to high concentration of virus in the air
  - Escape of virus laden air into stagnant corridors when room door is opened
  - Entry of virus laden air into nearby rooms when their residents subsequently open their doors

Wong, *Lancet Regional Health – Western Pacific* 2022;18:100360

How good is your surgical mask?

Medical Masks are Good! … But Not Perfect

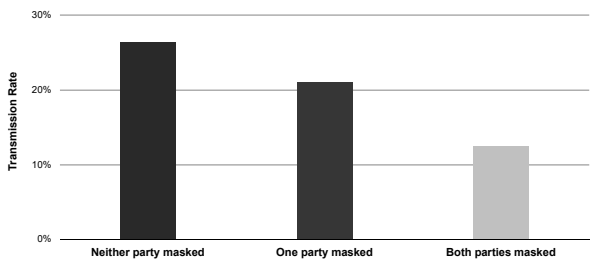
Transmission study using Golden Syrian Hamsters in adjacent cages with and without tightly fixed surgical masks between cages



Chan, Clin Infect Dis 2020;71:2139-2149

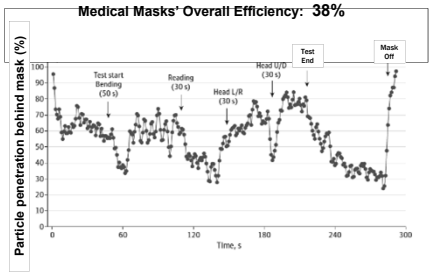
Masking Effectiveness in Practice

Transmission rates amongst 969 close contacts of 431 people with Covid-19, Johnson County Public Health, Iowa

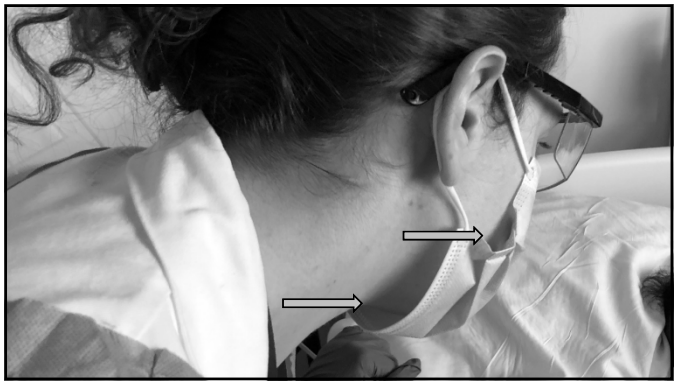


Riley, *Emerging Infectious Disease* 2021; doi: 10.3201/eid2801.211591

Mask Filtration Efficiency in Practice



Clapp, *JAMA Intern Med* 2020; doi: 10.1001/jamainternmed.2020.8168

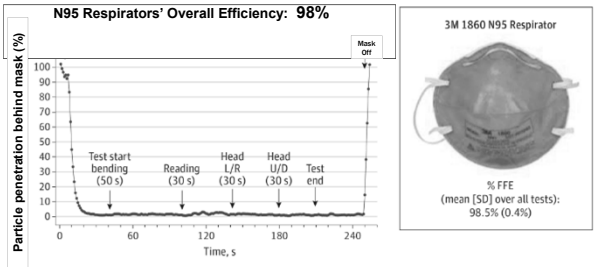


Transmission To and From HCWs Despite Masks

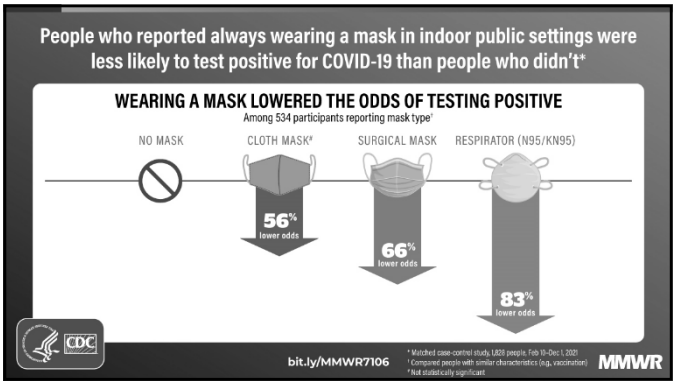
- We have documented multiple instances of transmission to healthcare workers despite masks & eye protection
- All transmissions confirmed by whole genome sequencing (0 SNP differences)
  - Patient to CT tech (10 min interaction)
  - Patient to video swallow technician (45 mins)
  - Asymptomatic inpatient to two patient care assistants (4-8 hours)
  - Presymptomatic nurse to patient (2 shifts)
  - Presymptomatic outpatient to physician (45 mins, both parties masked)

Klompas, *Ann Intern Med* 2021; doi.org/10.7326/M20-7567
Klompas, *Clin Infect Dis* 2021; doi.org/10.1093/cid/ciab218

We Have the Solution!



Sickbert-Bennett, *JAMA Intern Med* 2020; doi: 10.1001/jamainternmed.2020.4221.

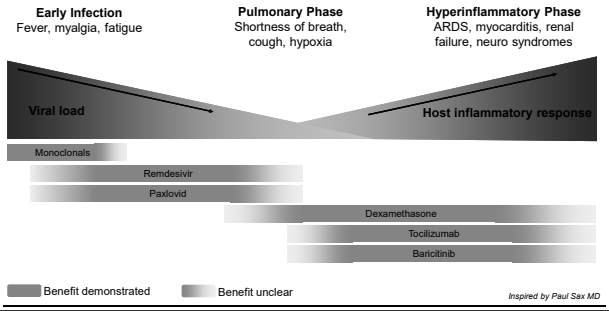


Question #6

Which of the following healthcare workers is at greatest risk of getting infected with SARS-CoV-2 by a patient?

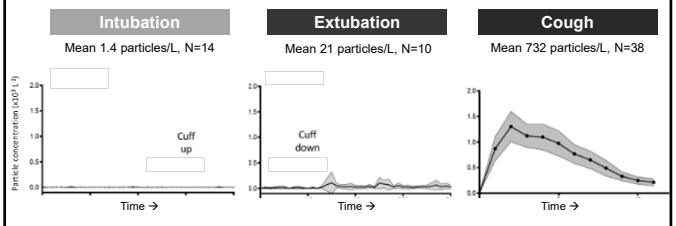
A. Anesthesiologist performing intubations for elective surgeries (patients tested within 72h of procedure, PPE = surgical mask)
B. Nurse working in a COVID ICU looking after patients on high flow O2 (PPE = N95, eye protection, gown, gloves)
C. Psychiatrist counselling healthy outpatients in person in her office (PPE = surgical mask)
D. Food services worker dropping off food trays for patients in Covid and non-Covid rooms. (PPE = surgical mask)

The Sickest are Sometimes the Least Contagious



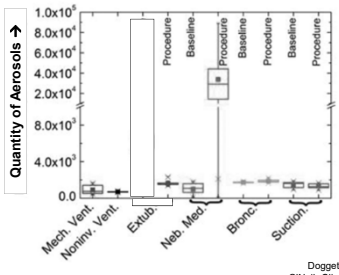
How many aerosols does intubation generate?

Continuous aerosol monitoring using an optical particle sizer in an operating room



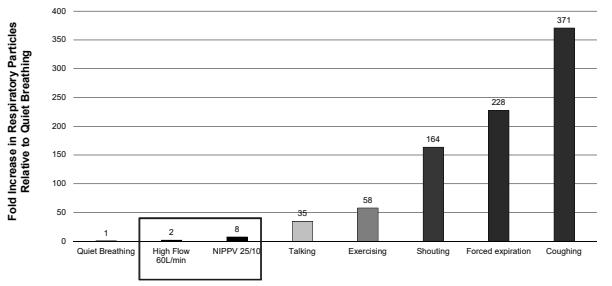
Brown, *Anesthesia* 2021;76:174-181

Most "Aerosol Generating Procedures" Do Not Generate Aerosols



Doggett, *Chest* 2020; 158:2467-2473
O'Neil, *Clin Infect Dis* 2017;65:1342-1348
Li, *Open Forum Infect Dis* 2017;4(Suppl 1):S34

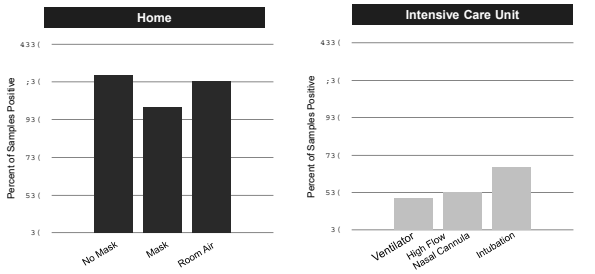
Impact of High Flow O2 on Respiratory Emissions



Wilson 2021, medRxiv, doi: 10.1101/2021.02.07.21251309

SARS-CoV-2 Air Sampling: ICU vs Home

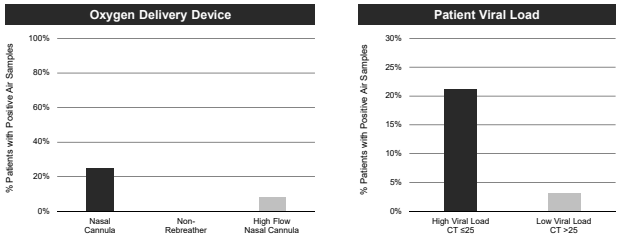
Air sampling for SARS-CoV-2 RNA in rooms of Covid positive patients in ICU vs home



de Man, J Hospital Infection 2021; doi: 10.1016/j.jhin.2021.10.018

Air Sampling for SARS-CoV-2

Room air samples obtained from 75 patients hospitalized with Covid-19; tested for SARS-CoV-2 RNA

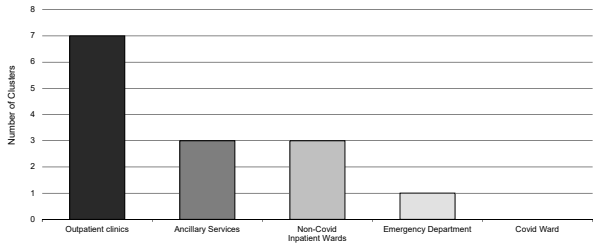


Air positivity for SARS-CoV-2 correlates with patient viral load, not with oxygen delivery device!

Janssen, *J Hosp Infection* 2022;123:87-91.

Where do nosocomial clusters occur?

Whole genome sequencing analysis of 14 clusters, 117 infections (112 HCWs, 5 patients), VA Northeast Ohio
Cluster defined as ≥3 potentially-related infections



Jinadatha, *Open Forum Infect Dis* 2021; doi.org/10.1093/ofid/ofab328

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

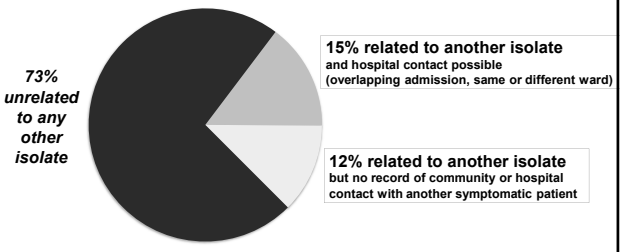
Question #7

A 63-year-old man with lymphoma is admitted for chemotherapy. His course is complicated by new atrial fibrillation and hospital acquired pneumonia (treated with vancomycin, cefepime, levofloxacin). On hospital day 12 he develops severe diarrhea and is diagnosed with *C. difficile* infection. Where did the patient most likely acquire this pathogen?

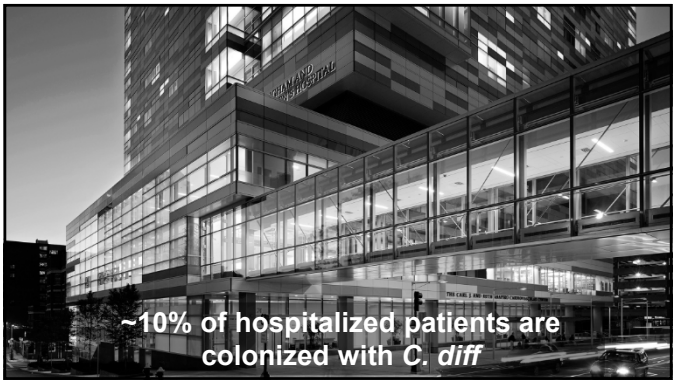
A. From another patient on his ward (carried by healthcare workers' hands)
B. From the toilet seat of the shared bathroom in his room
C. From the food provided by the hospital
D. From the community (already colonized on admission)

Where do patients get *C.difficile*?

Whole genome sequencing of 1,250 C. diff isolates from symptomatic inpatients & outpatients, Oxfordshire, UK, 2007-2011

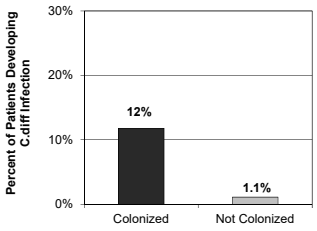


Eyre, *N Engl J Med* 2013;369:1195-1205



C.diff Colonization in ICU Patients and Progression to Infection

548 ICU patients at Johns Hopkins screened for C. difficile carriage on admission



Infect Control Hospital Epidemiol 2015;36:1324-1329

Risk of *C.diff* Acquisition Higher if Prior Room Occupant had *C.diff*

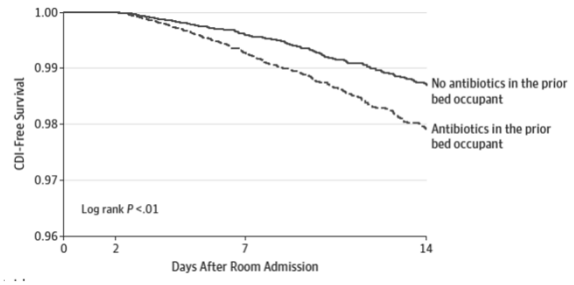
Medical ICU, University of Michigan Health System, 2005-2006

Prior Room Occupant Flagged for *C.diff*	**11.0%**
Prior Room Occupant Not Flagged for *C.diff*	**4.6%**

Adjusted Hazard Ratio **2.4** (95% CI 1.2-4.5)

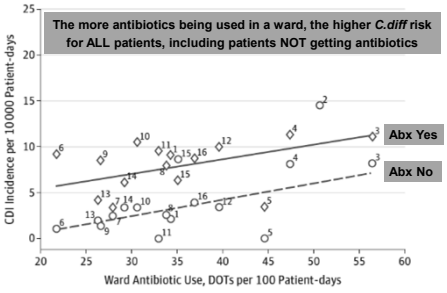
Infection Control Hospital Epidemiology 2011;32:201-206

Impact of Prior Bed Occupant's Antibiotic History and Current Bed Occupant's *C.diff* Risk



JAMA IM 2016;176:1801-1808

Ward Level Antibiotic Use and C.diff Risk



JAMA IM 2015;175:626-633

Question #8

2022 PREVIEW QUESTION

The MICU attending calls you because she's noticed 4 patients with new *Burkholderia cepacia* complex infections in her unit over the last 6 months. The patients were hospitalized during different periods and all were first detected >7 days after admission.
What potential sources will you investigate?

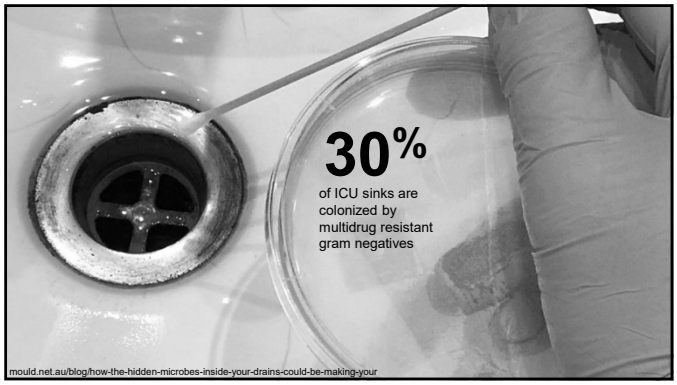
A. Are providers consistently washing their hands between patients?
B. Are providers wiping down stethoscopes & phones between patients?
C. Did all the patients receive care from a common healthcare worker?
D. Were there any common devices amongst patients (e.g. ventilators, ECMO, bronchoscopes, ultrasound probes, etc.)?
E. Did all the patients visit the same operating room?

Water avid pathogens

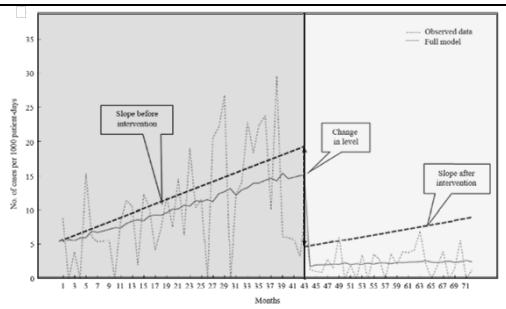
- *Burkholderia cepacia*
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- *Legionella pneumophila*
- *Serratia marcescens*
- *Non-tuberculous mycobacteria*
- *+/- Acinetobacter baumannii*
  Enterobacterales species

Think:

Respiratory care equipment
Contaminated sink drains
Contaminated medications
Heating & cooling devices
Decorative water displays
etc.



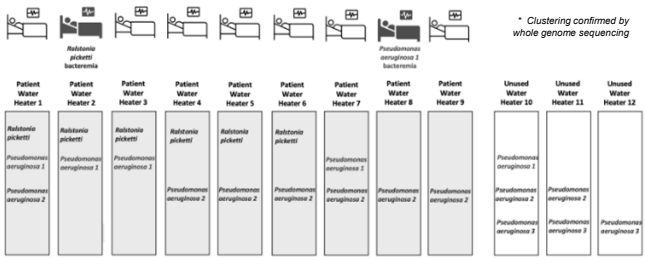
Drop in MDR Gram Negatives After Sink Removal



Shaw, J Hosp Infection 2018;98:275-281

Patient infections secondary to contaminated ECMO water heaters

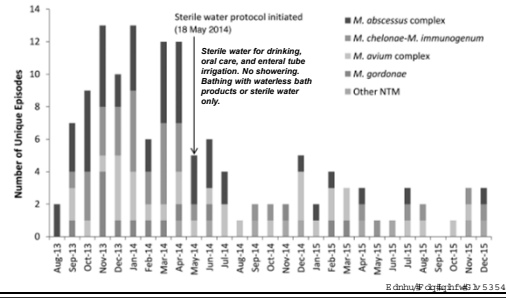
Ralstonia *and* ***Pseudomonas*** *bloodstream infections in 2 ECMO patients, Brigham & Women's Hospital, 2022*



Baker, *Clin Infect Dis* 2022:ePub ahead of print. doi: 10.1093/cid/ciac379

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



Question #9

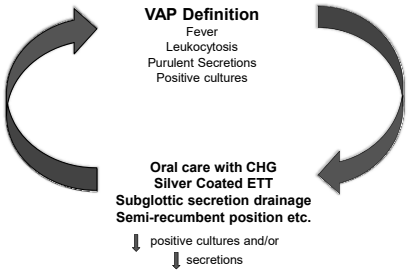
The CEO calls you to express her concern that ventilator-associated pneumonia rates in your hospital are double those of a competing hospital. Which of the following measures are advised to reduce ventilator-associated pneumonia rates and improve patient outcomes?

A. Silver coated endotracheal tubes
B. Oral care with chlorhexidine
C. Daily toothbrushing
D. Placing patients in the lateral Trendelenburg position
E. Probiotics

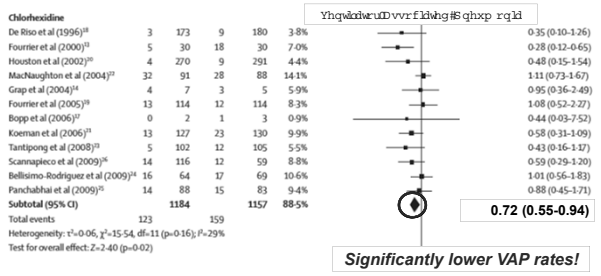
The VAP Prevention Paradox

	VAP Rates	Vent Days	ICU Days	Hospital Days	Death
Oral care with chlorhexidine	↓	—	—	—	—
Silver-coated endotracheal tubes	↓	—	—	—	—
Subglottic secretion drainage	↓	—	—	—	—
Head-of-bed elevation	↓	—	—	—	—

Circularity Between VAP Prevention Practices and the VAP Definition

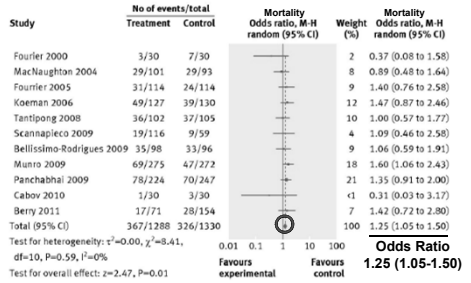


Oral Care with Chlorhexidine: Significantly *Lower* VAP Rates



Lancet Infectious Disease 2011;11:845

Oral Care with Chlorhexidine: Significantly *Higher* Mortality Rates



BMJ 2014;348:g2197

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 #10

You are part of a multidisciplinary team that has been working diligently to implement processes and practices to lower central line associated bloodstream infections in your hospital. Interventions to date include education, daily patient bathing with chlorhexidine, line insertion checklists, insertion kits, and maximal sterile barrier precautions during insertion. What additional steps should you consider implementing?

A. Create a standing order for vancomycin for all patients with central lines
B. Replace all central lines every 7 days
C. Preferentially site all lines in the internal jugular vein whenever possible
D. Require "double antiseptic" skin preparation with povidone-iodine-chlorhexidine before all insertions
E. Require "double antiseptic" skin preparation with alcohol-chlorhexidine before all insertions

Essential Practices to Prevent Line Infections

Before lqvhuwlrq

- Srvw#lqglfdwlrqv#iru#hylghqfh0edvhg# fhqwudo#olqh#xvh#wr#p lqlp l}h#xqqhfhvvdu|#xvh
- Surylgh#hgxfdwlrq#dqg#shuirup #frp shwhqf|#dvvhvvp hqw
- Gdlo|#edwklqj#zlwk#fkoruhh{lglqh

Lqihfwlrq#Frqwuro#)#Krvslwdo#Hslghp lrorj|#5355>76=88608<

Essential Practices to Prevent Line Infections

At insertion

- Use a checklist to assure all steps followed
- Perform hand hygiene
- Subclavian site preferred
- Use a catheter-placement kit with all necessary supplies
- Use ultrasound guidance to place the cathether
- Use maximal sterile barrier precautions
- Use an alcohol-chlorhexidine antiseptic for skin prep

Infection Control & Hospital Epidemiology 2022;43:553-569

Essential Practices to Prevent Line Infections

After insertion

- Ensure appropriate nurse:patient ratio and limit use of float nurses in ICUs
- Use chlorhexidine-containing dressings for central lines
- Change transparent dressings and perform site care with a chlorhexidine-based antiseptic q7d (or immediately if soiled)
- Disinfect catheter hubs, connectors, ports before each use
- Remove non-essential catheters promptly
- Replace administration sets q7d or less
- Routinely measure line infection rates and report back to unit staff & hospital leaders

Infection Control & Hospital Epidemiology 2022;43:553-569

Question #11

A 66 yo gent with poorly controlled diabetes is admitted with fever and a swollen left knee. He underwent elective knee replacement 3 weeks ago. Knee aspirate gram stain shows gram positive cocci in clusters. Culture is positive for Staph aureus (methicillin-susceptible). The patient is taken to the OR, the prosthesis is removed, and an antibiotic spacer is placed. The patient is devastated by the setback to his recovery and the need for more surgery. He asks what more could have been done to prevent this infection?

A. Obtain a urine culture before surgery to rule out occult bacteriuria
B. Screen all patients before arthroplasty to identify *Staph aureus* carriers and decolonize them with chlorhexidine + mupirocin
C. Prescribe 4 weeks of antibiotic prophylaxis for all arthroplasty patients
D. Only provide arthroplasty to patients with hemoglobin A1C's <7
E. Ensure all knee surgeries are performed with therapeutic hypothermia

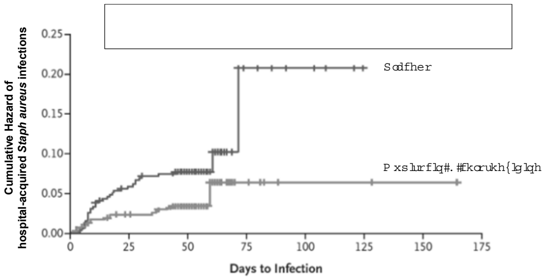
Best Practices to Prevent Surgical Site Infections

- Shower or bathe with soap or antiseptic before surgery
- Use antimicrobial prophylaxis before surgery only
- Use an alcohol-based agent for skin preparation
- Do not apply topical antimicrobials to the surgical incision
- Maintain blood glucose <200 mg/dL during surgery
- Warm patients to maintain normothermia during surgery
- Increase the fraction of inspired oxygen during surgery and after extubation in patients with normal pulmonary function

Berríos-Torres, JAMA 2017;152:784-791

Staph aureus screening & decolonization

917 hospitalized patients with positive Staph aureus nasal screens randomized to decolonization vs placebo



Bode, NEJM 2010;362:9-17

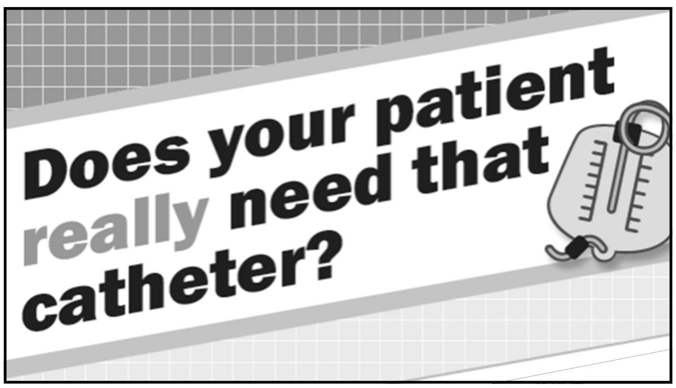
Question #12

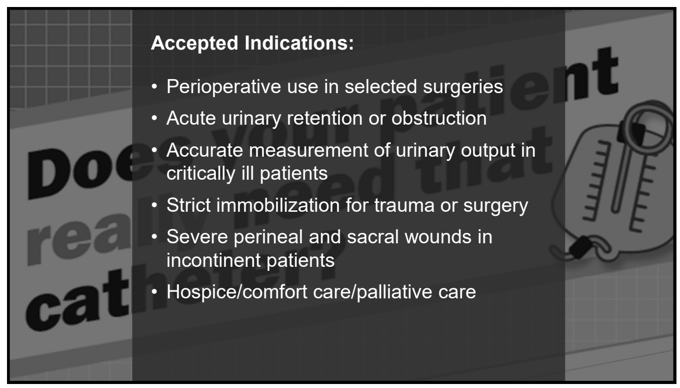
A 55 year old woman is emergently transferred to your hospital after falling and sustaining a spinal cord injury complicated by paraplegia. She is admitted to the intensive care unit following neurosurgery. You are driven to do all you can to protect her from hospital complications. Which of the following steps is most likely to reduce her risk of developing a catheter-associated urinary tract infection?

A. Start prophylactic Fosfomycin
B. Start prophylactic cranberry extrct
C. Change the urinary catheter every 7 days
D. Empty the catheter drainage bag before transporting her off the unit
E. Check a urinalysis daily and start pre-emptive antibiotics if she develops pyuria

Recommendations to Prevent CAUTI

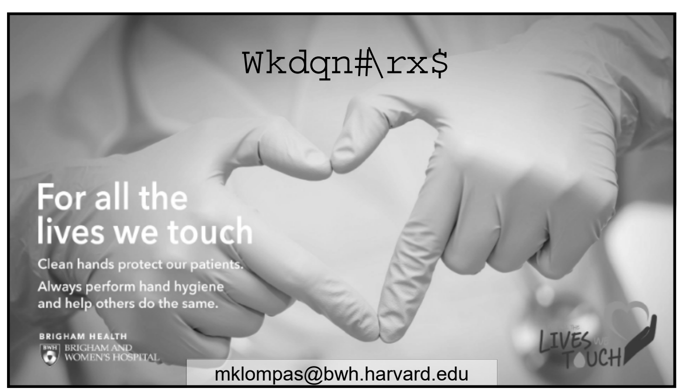
- Conduct daily assessment of the presence and need for indwelling urinary catheters
- Avoid using indwelling urinary catheters by using alternative urine-collection / measurements strategies
  - external suction catheters
  - condom catheters
  - daily weights for volume changes
  - bladder scanners
  - intermittent straight catheterization
- Aseptic technique for insertions
- Careful catheter maintenance
  - Xvh#d#forvhg#v|vwhp 1
  - Uhsodfh#li#euhdnv#lq#wkh#forvhg#v|vwhp
  - Nhhs#gudlqdjh#edj#ehorz#eodgghu
  - Hp sw|#edjv#t1vkliwdqg#ehiruh#wudqvsruw
  - Gr#qrw#suh0hp swlyho|#fkdqjh#fdwkhwhuv#wr# suhyhqw#lqihfwlrq
- Regular surveillance and feedback of infection rates





Summary

- Pneumonia is the most common hospital-acquired infection
- *C. difficile* is the most common hospital-acquired pathogen
- Hand hygiene rates are inversely associated with HAI rates
- Improving hand hygiene requires multimodal methods & "all hands on deck"
- Hands, clothing, and equipment commonly contaminated by bacteria
- Contact precautions are most effective against skin-based organisms
- Stopping contact precautions doesn't clearly increase infections but most studies to date have not looked at long term outcomes
- 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.
- Contaminated water, drains, respiratory equipment, and meds can spread water-based pathogens. Leading ICUs working on decreasing water-based care.



Agenda Day 3: Monday, August 22, 2022

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

24

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Dr. Khalil Ghanem

24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

6/29/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

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

GENITAL ULCER DISEASES (GUD)

- Syphilis (*Treponema pallidum*)
- HSV-2
- HSV-1
- Chancroid *(Haemophilus ducreyi)*
- Lymphogranuloma venereum (LGV) *(Chlamydia trachomatis)*
- Granuloma inguinale (Donovanosis) *(Klebsiella granulomatis)*
- Monkeypox

PAIN AND GUD

Which ulcers are PAINFUL?

- HSV
- Chancroid

Which ulcers are PAINLESS?

- Syphilis*
- LGV (but lymphadenopathy is PAINFUL)
- Granuloma inguinale

*** >30% of patients have multiple painful lesions**

"KEY WORDS" IN GUD

- SYPHILIS: Single, **painless** ulcer or chancre at the inoculation site with heaped-up borders & clean base; painless bilateral LAD **(>30% of patients have multiple painful lesions)**
- HSV: multiple, **painful**, superficial, vesicular or ulcerative lesions with erythematous base

24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

"KEY WORDS" IN GUD CONTINUED

- CHANCROID: painful, indurated, 'ragged' genital ulcers & tender **suppurative inguinal adenopathy** (50%); **kissing lesions** on thigh
- GI: **Painless**, progressive (destructive), **"serpiginous"** ulcerative lesions, without regional lymphadenopathy; beefy red with white border & highly vascular
- LGV: short-lived **painless** genital ulcer accompanied by **painful suppurative inguinal lymphadenopathy; "groove sign"**

QUESTION #1

A 35-year-old woman presents with a painless ulcer on her vulva and one on her soft palate following unprotected vaginal and receptive oral sex 3 weeks earlier. She has no other symptoms.

Examination reveals the two ulcers with heaped-up borders and a clean base.

QUESTION #1

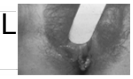
Which of the following diagnostic tests is **inappropriate** to obtain?

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

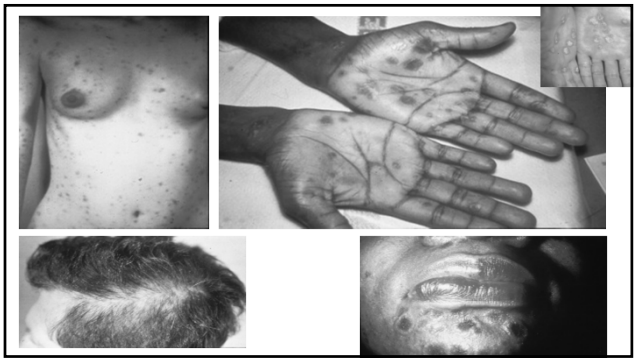
SYPHILIS: TAKE-HOME POINTS

- Neurological and ocular manifestations may occur during any stage of syphilis
- Both treponemal and non-treponemal tests may be nonreactive in primary syphilis but they are almost ALWAYS reactive in secondary and early latent syphilis (remember prozone reaction for non-treponemal test mainly in secondary syphilis)
- Treponemal tests are almost always reactive in late syphilis (once positive always positive) irrespective of treatment history
- Penicillin is the drug of choice to treat all stages of syphilis. No alternate agents should be used during pregnancy

EARLY SYPHILIS: CLINICAL MANIFESTATIONS



- Incubation ~3 weeks
- Primary: chancre; LAD; resolves 3-6 wks
- Secondary: **Systemic symptoms**: low-grade fever, malaise, sore throat, adenopathy
  - RASH: evanescent, copper-colored, macular (dry) rash; followed by a red papular eruption (involving palms and soles); mucosal lesions (gray plaques or ulcers) ; condyloma lata- wart-like lesions that develop in moist areas
  - Other manifestations: uveitis, patchy alopecia, hepatitis (mild elevation of aminotransferases with disproportionately high alkaline phosphatase), gastritis, periostitis, glomerulonephritis



24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

NEUROLOGICAL MANIFESTATIONS OF SYPHILIS

- **Can occur during any stage of infection**
- Can be either asymptomatic or symptomatic
- **Symptomatic Early Neurosyphilis**
  - Occurs within the **first year** after infection
  - **Mainly among PWH**
  - **Presents as meningitis** (headache; photophobia; cranial nerve abnormalities; ocular symptoms)
- Symptomatic Late Neurosyphilis (tertiary syphilis)
  - Usually occurs ~10 years AFTER primary infection
  - Divided into 2 categories:
    - Meningovascular
    - Parenchymatous

LATE NEUROSYPHILIS (TERTIARY)

Meningovascular

- Endarteritis of the small blood vessels of the meninges, brain, and spinal cord.
- Typical clinical manifestations include **strokes (middle cerebral artery distribution is classic)** and seizures

Parenchymatous

- Due to actual destruction of nerve cells
- **Tabes Dorsalis**: shooting pains, ataxia, cranial nerve abnormalities; optic atrophy
- **General Paresis**: dementia, psychosis, slurring speech; Argyll Robertson pupil

OTHER TERTIARY MANIFESTATIONS

Cardiovascular

- 15-30 years after latency
- Men 3X> women
- Aortic aneurysm; aortic insufficiency; coronary artery stenosis; myocarditis

~30% of patients with cardiovascular and gummatous syphilis will have asymptomatic neurosyphilis- perform CSF exam!

Late benign syphilis

- 'Gummas'
- Granulomatous process involving skin, cartilage, bone (less commonly in viscera, mucosa, eyes, brain)

SYPHILIS: EYES AND EARS

Eyes

- Ocular manifestation may occur during any stage and may involve any portion of the eye
  - Uveitis & neuroretinitis: mainly secondary stage
  - Interstitial keratitis: occurs in both congenital (typically at age 5-20; 80% bilateral) and acquired (both early and late infections)
  - **CSF examination normal in ~30% of cases of ocular syphilis**

Ears

- Sensorineural hearing loss w/vestibular complaints (sudden or fluctuating hearing loss, tinnitus or vertigo)
  - Congenital (early and late)
  - Acquired (secondary and late stages)
  - **CSF examination is normal in >90% of cases of otic syphilis**

*****No need for a CSF examination in patients who only have ocular or otic symptoms/signs**

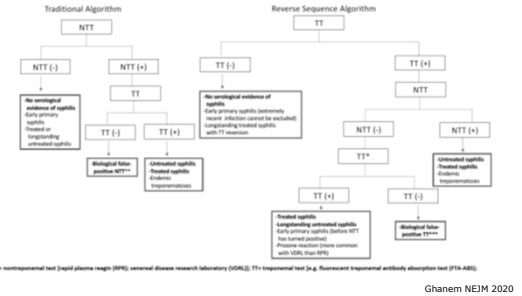
SYPHILIS SEROLOGICAL TESTING

Nontreponemal tests

- RPR (serum) or VDRL (serum or CSF)
- False+: endemic treponematoses, old age, pregnancy, autoimmune disease (APS), viral infections
- Reactive result must be confirmed with treponemal test
- False negative: PROZONE effect
- Four-fold (i.e. 2-dilution) decline after treatment = CURE (irrespective of the end-titer)
- **Titers will decline with or without treatment**

Treponemal tests

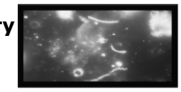
- MHA-TP, TPPA, FTA-Abs, EIAs, CIA
- Detect IgG +/- IgM antibodies against treponemal antigens
- **Once reactive, always reactive even after appropriate therapy**
  - **Exception: ~25% of persons treated early in primary syphilis may serorevert years later**
- False + may occur with endemic treponemal infections (e.g. yaws, pinta, bejel), with Lyme disease, or rarely in autoimmune conditions



Ghanem NEJM 2020

SYPHILIS: DIAGNOSTICS

- Darkfield microscopy or PCR for **genital** ulcers of primary syphilis; **sensitivity of serology in primary syphilis only~70%**
- **Sensitivity of serology for secondary or early latent syphilis ~100%**
- Over time, non-treponemal serological titers decline and may become nonreactive even in the absence of therapy while treponemal titers remain reactive for life*



NEUROSYPHILIS: DIAGNOSTICS

- No single test can be used to diagnose neurosyphilis
  - 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 test

SYPHILIS THERAPY

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
  - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks

SYPHILIS THERAPY CONTINUED

- Neurosyphilis/Ocular/Otic syphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Procaine penicillin 2.4 MU IM qd + probenecid 500 mg po QID X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days (2nd line regimen)
- Jarisch-Herxheimer: within 6 hours (up to 24 hours) after therapy of (usually) early syphilis; antipyretics only; **<u>may induce early labor</u>**

QUESTION #2

PREVIEW QUESTION

A pregnant patient living with HIV(CD4 260 cells/mm^3; HIV RNA <50 copies/ml) on ART presents with a diffuse rash.

On examination, she has a temperature of 38.3°C and a macular rash on her trunk and extremities including her palms.

Serum RPR is reactive at a titer of 1:2048 and FTA-ABS is reactive

She has a history of severe hives to penicillin but has tolerated cephalosporins.

QUESTION #2

PREVIEW QUESTION

Which of the following antibiotics is most appropriate?

A. Azithromycin
B. Benzathine penicillin G
C. Ceftriaxone
D. Doxycycline

24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

SYPHILIS & HIV

- Clinical manifestations similar but timeline may be compressed
  - PWH more susceptible to early neurosyphilis
- Testing and therapy similar to HIV negative
- Serological failure is more likely among PWH
- Serological response may be slower among PWH
- Follow-up is more frequent (every 3 months)

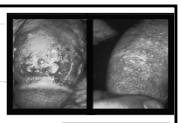
SYPHILIS & PREGNANCY

- Screen at 1st prenatal visit
- Screen higher risk patients and those living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- Screen all those who deliver a stillborn infant after 20 weeks' gestation
- **Pregnant penicillin-allergic patients with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)**

HSV TAKE-HOME MESSAGES

- Both HSV-1 (particularly among young women and MSM) and 2 cause genital infections
- Most people are unaware that they are infected
- Asymptomatic shedding is the most common reason for transmission
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations
- C-section ONLY in those who have active lesions or prodromal symptoms at the time of delivery

HSV



- 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: 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!**

24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

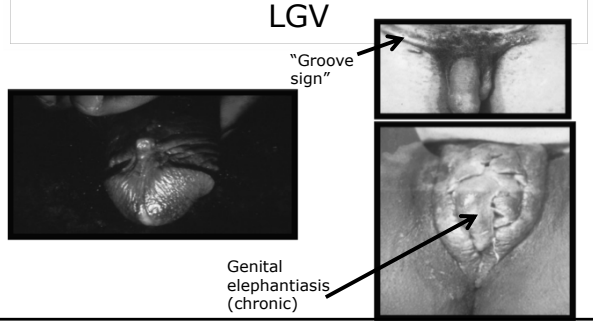
HSV: PREGNANCY

- Risk of vertical transmission if mom acquires FIRST episode (i.e. primary infection) of herpes at time of delivery= up to 80%
- Risk of vertical transmission if mom has RECURRENT episode of herpes at time of delivery <1%
- C-sections are recommended ONLY IF ACTIVE LESIONS OR PRODROMAL SYMPTOMS (i.e. vulvar pain/burning) PRESENT AT DELIVERY
  - ACOG: "For women with a primary or nonprimary first-episode genital HSV infection during the 3rd trimester of pregnancy, cesarean delivery MAY BE OFFERED due to the possibility of prolonged shedding". ACOG Practice Bulletin #220, May 2020
- Efficacy data on routine acyclovir use during 3rd trimester of pregnancy to prevent HSV vertical transmission are lacking.
  - ACOG: Those with a clinical history of genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation ACOG Practice Bulletin #220, May 2020 & Cochrane Systematic Review 2008: https://doi.org/10.1002/14651858.CD004946.pub2

CHLAMYDIA TRACHOMATIS L1-L3: LGV

- Classical manifestation is a short-lived **painless** genital ulcer accompanied by **painful** inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with **proctitis** particularly among MSM**********
  - Rectal pain, tenesmus, rectal bleeding/discharge
  - May be mistaken for inflammatory bowel disease histologically (early syphilitic proctitis may also be mistaken for IBD on histology)

LGV

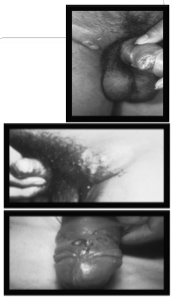


LGV DIAGNOSIS & THERAPY

- **Routine NAATs** do not distinguish between serotypes D-K and L1-L3 (LGV). **Multiplex PCR** can be performed for specific serotypes but is NOT commercially available. Serology is NOT standardized and is NOT recommended
- Therapy: **doxycycline 100mg PO BID X 3* weeks (preferred)** or azithromycin 1g PO q week X 3 weeks (alternate)
- Patients with *C trachomatis* + 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

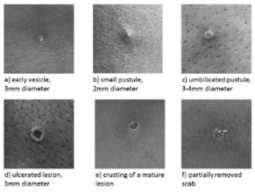
- *Klebsiella granulomatis (Calymmatobacterium granulomatis)*
- Not endemic in US; common in SE Asia (India), & Southern Africa (recently eradicated in Australia)
- Painless, progressive (destructive), "serpiginous" ulcerative lesions, without regional LAD (pseudobuboes occasionally); beefy red with 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)

24 – Sexually Transmitted Infections: Genital Ulcers Diseases (GUD)

Speaker: Khalil Ghanem, MD

MONKEYPOX

- Prodrome: Fever, chills, rash, or new lymphadenopathy; however, onset of perianal or genital lesions (often painful) in the absence of prodrome may occur; proctitis described
- DDx rash: Secondary syphilis, HSV, chancroid, and VZV. Consider in men who report sexual contact with other men (incubation 5-21 d) & individuals reporting a significant travel history
- Patients generally describe close, sustained physical contact with other people with monkeypox (respiratory transmission inefficient)
- Persons are infectious once symptoms begin; when all scabs have fallen off a person is no longer contagious
- Rx: Tecovirimat (CDC-held Emergency Access Investigational New Drug Protocol)



UK Health Security Agency

GUD	Pain	Characteristics	Diagnosis	Treatment
HSV 1 & 2	Painful	Multiple, superficial, vesicular/ulcerative, erythematous base	-NAATs -Culture (sensitivity ~70%) -Serology	-Acyclovir etc. -Foscarnet (resistant HSV) -Cidofovir parenteral or topical (resistant HSV)
Syphilis (T. pallidum)	Painless	Single, well circumscribed, heaped-up borders, clean base	- Serology - PCR	-Penicillin (preferred) -Doxycycline (alternate for early and late latent)
Chancroid (H. ducreyi)	Painful	Indurated, tender suppurative inguinal LAD (50%); kissing lesions on thigh	- Culture - PCR	-Azithromycin -Ceftriaxone -Erythromycin -Ciprofloxacin
LGV (C. trachomatis)	Painless	short-lived ulcer, painful suppurative LAD, "groove sign" PROCTITIS	- NAATs - Serology - Culture (rarely)	-Doxycycline (preferred) -Azithromycin (alternate)
Granuloma Inguinale (Klebsiella granulomatis)	Painless	Progressive "serpiginous" without LAD; beefy red with white border & highly vascular	- Biopsy	-Doxycycline -Azithromycin -Bactrim

25

Infections of Upper and Lower Urinary Tract

Dr. Barbara Trautner

25 – Infections of Upper and Lower Urinary Tract

Speaker: Barbara Trautner, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Urinary Tract Infections

Barbara W. Trautner, MD, PhD
Professor of Medicine
Baylor College of Medicine

6/21/2022

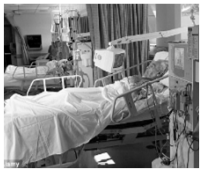
INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Genentech for COVID-related research

Topics to cover

- Acute cystitis in women
- Asymptomatic bacteriuria
  - Pregnant women
  - Renal transplant
  - Pre-operative screening
- Catheter-associated UTI
- Urosepsis and worse
  - Emphysematous pyelonephritis
  - Emphysematous cystitis
  - Xanthogranulomatous pyelonephritis



UTI differs in different populations

UTI is not the same entity in these different populations
Symptoms and management differ

UTI Question #1

A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms three months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. Bactrim
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

Current IDSA UTI Guidelines*

*update in progress

These guidelines cover:

- Uncomplicated cystitis
- Uncomplicated pyelonephritis
- Premenopausal women
- Primarily outpatients

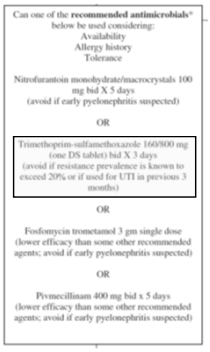
IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

IDSA Cystitis Guidelines (2010)

First-line agents
- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin

Alternative choices
- Fluoroquinolones
- Beta-lactams


Can one of the **recommended antimicrobials*** below be used considering:
Availability
Allergy history
Tolerance

Nitrofurantoin monohydrate/macrocrystals 100 mg bid X 5 days
(avoid if early pyelonephritis suspected)

OR

Trimethoprim-sulfamethoxazole 160/800 mg (one DS tablet) bid X 3 days
(avoid if resistance prevalence is known to exceed 20% or if used for UTI in previous 3 months)

OR

Fosfomycin trometamol 3 gm single dose
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

OR

Pivmecillinam 400 mg bid x 5 days
(lower efficacy than some other recommended agents; avoid if early pyelonephritis suspected)

How long do you treat acute cystitis?

First line choices (5, 3, 1)
- Nitrofurantoin X 5
- Trimethoprim/sulfamethoxazole X 3
- Fosfomycin X1

IDSA Guidelines on Uncomplicated Cystitis, 2010

JAMA Network

From: **Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial**

JAMA. 2018;319(17):1781-1789. doi:10.1001/jama.2018.3627

Table 3. Clinical and Microbiologic Outcomes

Clinical and Bacteriologic Outcome	No./Total No. (%) Nitrofurantoin (n = 255)	Fosfomycin (n = 258)	Difference, % (95% CI)	*P* Value[a]
Primary Outcome				
Clinical response at 28 d[b]				
Clinical resolution	171/244 (70)	139/241 (58)	12 (4-21)	.004
Clinical failure	66/244 (27)	94/241 (39)		
Indeterminate	7/244 (3)	8/241 (3)		
Missing[c]	11 (4)	17 (7)		

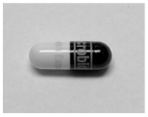
Clinical and microbiological response to 5 days of nitrofurantoin was better than to single dose fosfomycin

Nitrofurantoin: Clinical use

- Interferes with several aspects of bacterial metabolism
- *E. coli* resistance uncommon
- Great for *E. coli* cystitis and prophylaxis
- Inadequate levels in tissue and blood
- Dyes urine yellow
- Intrinsic resistance in *Pseudomonas, Proteus, Serratia*
- Resistance frequent in *Klebsiella* and *Enterobacter*
- Renal excretion but OK to use if GFR >30 mL/min

Cunha et al, Eur J Clin Microbiol Infect Dis 2017; 36(7)
Singh, CMAJ 2015; 187(9)
AGS Beers Criteria 2019

Nitrofurantoin Adverse Events



- Pulmonary toxicity--RARE
  - Acute: reversible hypersensitivity reaction
  - Chronic: persistent pulmonary fibrosis
    - Dose dependent?
    - Favors use of lowest possible dose/less frequent dosing for chronic prophylaxis
- Hepatitis—RARE
- Nausea—common
  - Worse with micro- (QID) than macro-crystalline (BID) formulation

Santos, JAGS 2016, PMID: 27100576

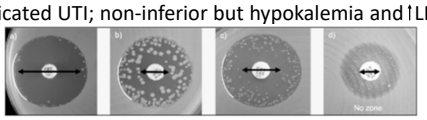
Fosfomycin: Mechanism and Susceptibility Testing

- Inhibits peptidoglycan synthesis
- Requires uptake into the bacterial cell via transporter
- Susceptibility testing
  - G6PD must be present
  - MIC breakpoints standardized ONLY for urinary *E. coli*
  - Requires disk diffusion
- Registered in US in 1996 to treat cystitis caused by *E. coli* and *E. faecalis*
- IV form available in Europe but not United States
- Variable susceptibility in *Klebsiella*, *Pseudomonas*
- Resistant: *Acinetobacter*
- Resistance: mainly loss of uptake, some inactivation

Silver, Cold Spring Harbor Perspectives in Medicine 2017

Fosfomycin: Clinical use for UTI

- High levels in urine for over 24 hours
- Single 3 gm dose for cystitis
- Developing niche for ESBL- and KPC- Enterobacteriaceae
  - 3gm every 48-72 hours
- ZEUS trial: IV fosfomycin versus piperacillin-tazobactam for complicated UTI; non-inferior but hypokalemia and↑LFTs



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

Potential harms of quinolones: FDA warnings

- Dysglycemia
- Tendon rupture/damage
- Interstitial nephritis
- Neuropathy
- Diarrhea—with or without *C. diff*
- Aortic aneurysms?
- Arrhythmias

FDA WARNING

Safety Announcement

[05-12-2016] The U.S. Food and Drug Administration is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.

"Treatment" of Cystitis with NSAIDS

- Randomized double-blind trial of diclofenac versus norfloxacin
- 253 women with symptoms of uncomplicated cystitis
  - 73% culture positive
  - 70% of organisms sensitive to norfloxacin
- Norfloxacin was superior to diclofenac for
  - Symptom resolution at 3 days (80% versus 54%)
  - Time to resolution of symptoms (2 versus 4 days)
  - Pyelonephritis prevention (0 cases versus 6, or 5%)

Kronenberg et al, BMJ 2017

UTI Question #1

A 24-year-old woman is evaluated for cystitis symptoms of 3 days' duration. She reports no fever, chills, flank pain, or vaginal discharge. She had similar symptoms two months ago and was treated with trimethoprim-sulfamethoxazole, with relief of symptoms.

On physical examination, vital signs and other findings are unremarkable.

On microscopic urinalysis, leukocytes are too numerous to count, erythrocyte count is 10/hpf, 4+ bacteria are present, and rare squamous epithelial cells are seen. Urine pregnancy test is negative.

Which of the following is the most appropriate management?

A. Nitrofurantoin-best choice for uncomplicated cystitis when TMP/SMX not an option
B. Bactrim (or TMP/SMX)—she had this recently, so may now have resistance
C. Fosfomycin—would be fine, not commonly used in US and may cost more
D. Ciprofloxacin—avoid when other options available
E. Ibuprofen—slower to relieve symptoms and less effective at preventing pyelonephritis

UTI Question #2

A 69-year-old woman comes in for an annual checkup. No change in her baseline health status. When she coughs or sneezes, she notes slight leakage of urine. Her medical history is significant for three vaginal births, and she has well-controlled hypertension.

Her BMI is 30. Her vital signs and other physical examination findings are normal.

On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

Which of the following is the most appropriate management?

A. Nitrofurantoin
B. Ciprofloxacin
C. Cystoscopy
D. Urine culture and sensitivities
E. No further infectious workup

Prevalence of Asymptomatic Bacteriuria

Population	Prevalence, %
Children	
Boys	<1
Girls	1–2
Healthy women	
Premenopausal	1.0–6.0
Pregnant	1.9–9.5
Postmenopausal (age 50–70 y)	2.6–8.6
Persons with diabetes	
Women	10.8–16
Men	0.7–11
Elderly persons in the community (age ≥70 y)	
Women	10.8–16
Men	3.6–19
Elderly persons in a long-term care facility	
Women	25–50
Men	15–50
Persons with spinal cord injury	
Intermittent catheter use	23–89
Sphincterotomy/condom catheter	57
Persons with kidney transplant	
First month posttransplant	23–24
1 mo–1 y post-transplant	10–17
>1 y post-transplant	2–9
Persons with indwelling catheter use	
Short-term	3%–5%/day catheter
Long-term	100

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

Guidelines on Screening for ASB in Pregnant Women

Agency	Year	Recommended?	Strength?	When?	How?	Desired Outcomes
IDSA (United States)	2019	Yes	Strong	12-16 weeks	Culture	Decreased pyelonephritis, decreased low birth weight Possible decrease in preterm labor
CTFPHC (Canadian)	2018	Yes	Weak	1st trimester	Culture	Decreased pyelonephritis, decreased low birth weight
USPSTF (United States)	2019	Yes	Grade B	12-16 weeks or first prenatal visit	Culture	Decreased pyelonephritis, decreased low birth weight

Treatment of ASB and Cystitis During Pregnancy

Antibiotic	Dose	Duration	Notes
Nitrofurantoin	100 mg orally every 12 hours	Five to seven days	Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected. Avoid use during the first trimester and at term if other options are available.
Amoxicillin	500 mg orally every 8 hours or 875 mg orally every 12 hours	Five to seven days	Resistance may limit its utility among gram-negative pathogens.
Amoxicillin-clavulanate	500 mg orally every 8 hours or 875 mg orally every 12 hours	Five to seven days	
Cephalexin	500 mg orally every 6 hours	Five to seven days	
Cefpodoxime	100 mg orally every 12 hours	Five to seven days	
Fosfomycin	3 g orally as single dose		Does not achieve therapeutic levels in the kidneys so should not be used if pyelonephritis is suspected.
Trimethoprim-sulfamethoxazole	800/160 mg (one double strength tablet) every 12 hours	Three days	Avoid during the first trimester and at term.

The durations listed in the table are based on data from studies conducted in both nonpregnant and pregnant women.

UpToDate

Treatment should be culture based
Group B strep bacteriuria calls for prophylaxis at delivery

UpToDate 2022, Hooton and Gupta

IDSA Guidelines on ASB 2019

Screening and Treatment Indicated

- ✓ Pregnant women
- ✓ Prior to urologic surgery with mucosal trauma
  - Pre-operative urine culture recommended
  - Treat with 1-2 doses of antibiotics shortly prior to surgery

Screening and Treatment Discouraged

- X Infants and children
- X Non-pregnant women
- X Functionally-impaired older adults
- X Diabetic adults
- X Patients >1 month from kidney transplant
- X Neutropenic patients
- X Patients with solid organ transplant
- X Persons with spinal cord injury
- X Patients with indwelling catheters
- X Prior to non-urologic surgery

Mythbusting: Which of the following is true?

A. A change in urine color is an indication for a urine culture
B. Bad smelling urine is suggestive of a UTI
C. Sediment in the urine means we should change the catheter
D. The level of pyuria helps in diagnosis of catheter-associated UTI
E. Beets can turn urine red

UTI Question #3

A 75-year-old man is seen in the pre-operative clinic. He is scheduled to undergo cystoscopy and possible biopsy for persistent hematuria. He is also scheduled for elective left total knee replacement, shortly after the urinary procedure. Other than the hematuria, he denies urinary-specific symptoms. He underwent kidney transplantation 3 years earlier, related to complications of diabetes.

On physical examination, vital signs are normal. His left knee has an effusion but is not red or excessively painful. No change in his baseline creatinine clearance.

On urinalysis, leukocyte count is 10/hpf, erythrocyte count is 100/hpf, 4+ bacteria are present, and no squamous epithelial cells are seen. Urine culture grew >10,000-<100,000 colony-forming units of *Klebsiella pneumoniae*.

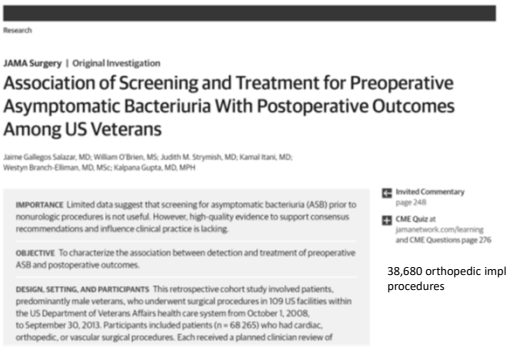
Kidney ultrasonography is unremarkable.

Which of the following is the primary indication for antimicrobial therapy in this patient?

A. Cystoscopy and biopsy
B. Diabetes mellitus
C. Kidney transplant
D. Knee prosthesis placement

Preoperative screening for ASB

New(ish) evidence!



Research

JAMA Surgery | Original Investigation

Association of Screening and Treatment for Preoperative Asymptomatic Bacteriuria With Postoperative Outcomes Among US Veterans

Jaime Gallegos Salazar, MD; William O'Brien, MS; Judith M. Strymish, MD; Kamal Itani, MD; Westyn Branch-Elliman, MD, MSc; Kalpana Gupta, MD, MPH

IMPORTANCE Limited data suggest that screening for asymptomatic bacteriuria (ASB) prior to nonurologic procedures is not useful. However, high-quality evidence to support consensus recommendations and influence clinical practice is lacking.

OBJECTIVE To characterize the association between detection and treatment of preoperative ASB and postoperative outcomes.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study involved patients, predominantly male veterans, who underwent surgical procedures in 109 US facilities within the US Department of Veterans Affairs health care system from October 1, 2008, to September 30, 2013. Participants included patients (n = 68 265) who had cardiac, orthopedic, or vascular surgical procedures. Each received a planned clinician review of

Invited Commentary page 248

CME Quiz at jamanetwork.com/learning and CME Questions page 276

38,680 orthopedic implant procedures

Preoperative Screening for ASB: Key Findings

- Of 17,749 preoperative urine cultures
  - 755 positive
  - 617 were ASB
- ASB did not increase odds of surgical site infection (SSI)
- In 2 cases the urinary organism matched the organism causing SSI (*Staph aureus*)
- ASB was associated with an increased risk of UTI
- Treatment of ASB
  - Not associated with lower risk of surgical site infection
  - Not associated with lower odds of UTI

UTI Question #4

A 46-year-old man is admitted to the hospital for urgent repair of aortic dissection. An indwelling urinary catheter is inserted prior to surgery. Endovascular aortic aneurysm repair is successful, and he is transferred to the surgical intensive care unit. He has underlying diabetes and systolic heart failure.

In addition to removing the urinary catheter as soon as possible, which of the following will decrease this patient's risk of catheter-associated urinary tract infection?

A. Daily cleansing of the meatal area of the catheter with antiseptics
B. Routine catheter change every 3 days
C. Screening for and treatment of bacteriuria
D. Keeping the collecting bag below the level of the bladder
E. Use of antiseptic- or antibiotic-coated urinary catheters

CAUTI prevention

- Do remove the urinary catheters when possible
  - Only indwelling Foleys count for CAUTI metrics
  - ALL types of urinary catheters are associated with bacteriuria
- Don't culture the urine in asymptomatic patients
- Do follow aseptic insertion
- Do ensure uninterrupted drainage
  - No tugging
  - No kinking
  - No reflux due to elevated drainage bag
- Don't routinely irrigate the bladder, exchange the catheter, or use antimicrobial catheters

https://www.cdc.gov/infectioncontrol/guidelines/cauti/

UTI Question #5

A 78-year-old woman is transferred to the surgical ICU after undergoing repair of a urethral diverticulum. The procedure was performed under spinal anesthesia, but difficulties with hypotension during the procedure led to her receiving 2L of IV fluids. She has underlying CHF and renal insufficiency. She arrives in the ICU with an indwelling Foley catheter, placed during the procedure. Prior to the procedure, she had limited mobility and urinary incontinence. She has a stage 1 sacral ulcer (redness but no skin breakdown).

Which of the following is **NOT** an appropriate reason to leave her indwelling catheter in place?

A. Assessment of her urinary output
B. Urinary retention from the spinal anesthesia
C. Management of incontinence
D. Recent surgery on the urethra

Indications for indwelling Foley catheters

Appropriate
- Monitor urine output in critically ill patients
- Acute urinary retention
- Certain surgical procedures (urologic, long duration, large volume shifts)
- Prolonged immobilization from fracture/trauma
- Healing open pressure ulcer
- End of life comfort

Inappropriate
- Prevention of pressure ulcers
- Management of incontinence
- Urine culture collection
  - (use in and out if needed)

https://www.cdc.gov/infectioncontrol/pdf/guidelines/cauti-guidelines-H.pdf

UTI Question #6

68-year-old diabetic man with CHF, vascular disease, BPH presented with 2 days of vomiting, abdominal pain, and confusion.

Vital signs: T 99.9 BP 47/39, HR 110, RR 22

Physical exam: patient was obtunded but appeared to have tenderness in the epigastric area

Labs: WBC 23.7 (94% segs), platelets 96K; Creatinine 3.1 (from 1.7 baseline)

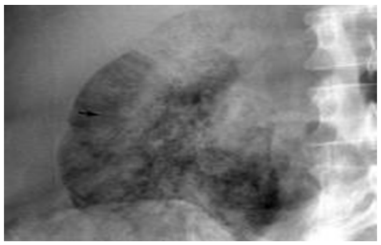
UA: WBC 250, RBC too numerous to count, no bacteria

Troponin 7.2, EKG with ST elevations; HgB A1c 10.5

He was admitted to the CCU and initiated on therapy for an ST elevation myocardial infarction. His blood pressure was labile, and he required pressor support. He required intubation. On hospital day 2, his blood cultures grew 4/4 bottles of *Klebsiella pneumoniae*.

The next slide shows an abdominal radiography (KUB) that had been performed at admission.

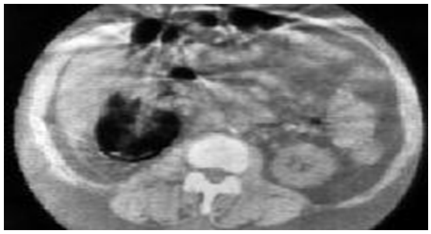
KUB X-Ray of Abdomen



What would you order next?

A. Abdominal ultrasound
B. Abdominal CT
C. Nasogastric tube
D. Stool for *C. diff* testing

Answer: Abdominal CT



Emphysematous pyelonephritis: CT showing gas within the renal parenchyma is definitive

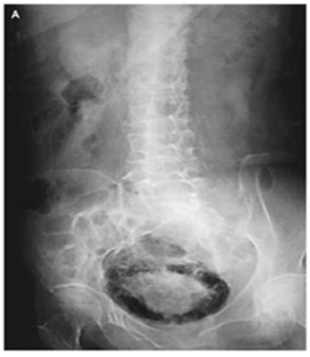
Clinical course of case #6

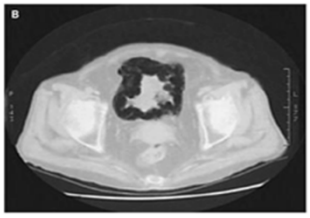
- Percutaneous drainage of the right kidney
- Renal drainage grew *Klebsiella*
- After weeks in the ICU was stable enough for nephrectomy
- 9 months later had then CABG

Diagnosis and management of emphysematous pyelonephritis

- 95% of cases in patients with diabetes (poorly controlled)
- Negative prognostic factors: shock, impaired consciousness, thrombocytopenia, renal failure
- Organisms: *E. coli, Klebsiella, Proteus*
- Diagnosis often delayed
- Differential: renal abscess, papillary necrosis
- Radiological diagnosis
- **Managed initially by drainage**—percutaneous nephrostomy or ureteral stent
- Nephrectomy for non-responders, severe cases

Kamei, J Infection and Chemotherapy 2021

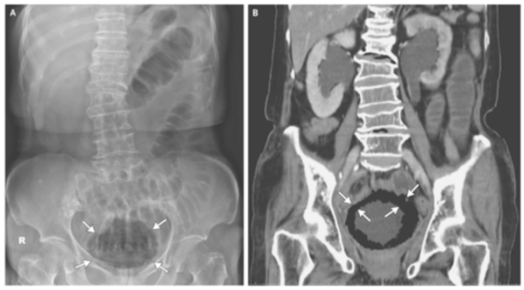




Emphysematous cystitis

Asada, NEJM 2003;349: 258

Emphysematous Cystitis



Tzou, NEJM 2016: 375; 18

Diagnosis and management of emphysematous cystitis

- Female predilection
- Most cases in diabetics
- Commonly caused by *E. coli, Klebsiella* (*Candida* reported)
- Organisms produce gas in the bladder wall and lumen
- Can present with lower abdominal pain
- Diagnosed radiologically
- Relieve bladder obstruction if present
- Typically responds well to **medical management**

UTI Question #7

57-year-old man with spinal cord injury (T12) and a chronic indwelling urinary catheter. Two years prior he had a fever, and his blood grew *S. aureus* and *Pseudomonas*. Urine grew lactose negative GNR and gram-positive organisms.

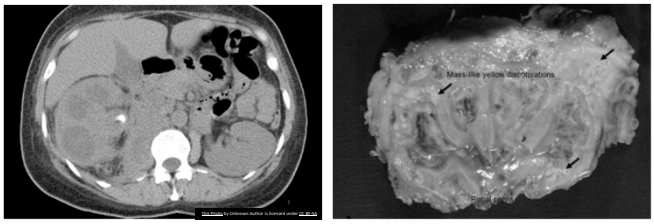
One year prior, he again had a fever, and his blood grew *Serratia, E. coli,* and *Pseudomonas*. Urine grew *Serratia* and *Pseudomonas*.

Both times he was treated with appropriate antibiotics, with resolution of fever and stabilization.

He has had many urine cultures, all of which grew multiple urinary pathogens.

Prior to entry in a research protocol, he had a screening abdominal ultrasound, which showed a hypoechoic mass in right kidney. In addition to CT scan, what will be the definitive therapy:

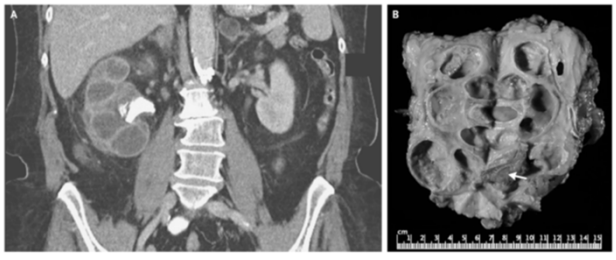
A. Renal biopsy
B. 3-6 months of antibiotics based on current urine culture
C. Percutaneous drainage
D. Nephrectomy



Xanthogranulomatous pyelonephritis

https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

Xanthogranulomatous Pyelonephritis



Bear paw sign

Marinacci, New England Journal of Medicine 2018; 378:10

Xanthogranulomatous pyelonephritis

- Chronic polymicrobial infection of renal parenchyma
- Often starts with stone/obstruction
- Frequently insidious and mistaken for tumor
- Renal tissue is destroyed and replaced by granulomatous tissue
- Yellow from the foam cells (macrophages) full of lipids
- **Requires nephrectomy** plus antibiotics

- Our patient underwent right nephrectomy, with finding of a variegated tan-white mass, large amount of inflammatory reaction, purulence in right renal fossa

To Re-Cap

- Acute cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women-screen and treat
  - Renal transplant-do **not** screen or treat
  - Pre-operative screening-**not** indicated unless urologic surgery
- Catheter-associated UTI—ensure unobstructed drainage
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

Is everything clear now?

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- @bwtrautner

26

Sexually Transmitted Infections: Other Diseases and Syndromes

Dr. Khalil Ghanem

26 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Sexually Transmitted Infections: Other Diseases and Syndromes

Khalil G. Ghanem, MD, PhD
Professor of Medicine
Division of Infectious Diseases
Johns Hopkins University School of Medicine

6/29/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

OF NOTE

- I have tried to use patient-first language throughout. When the terms 'women' and 'men' are used, I am referring to cis-gender women and men unless otherwise specified
- All photos are freely available from the following website unless otherwise noted: http://www.cdc.gov/std/training/clinicalslides/slides-dl.htm

OTHER STI SYNDROMES

- Urethritis/Cervicitis/Vaginitis
- Proctitis
- PID
- Epididymitis
- HPV
- Ectoparasites

URETHRITIS/CERVICITIS/VAGINITIS

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*
- *Trichomonas vaginalis*
- Bacterial vaginosis

QUESTION #1

IDBR 2022 PREVIEW QUESTION

A 32-year-old man presents complaining of a penile discharge. Gram's stain of the urethral discharge reveals intracellular Gram-negative diplococci. He reports an allergy to penicillins and cephalosporins. Which of the following regimens does the CDC recommend as the most appropriate therapy?

A. Azithromycin
B. Azithromycin plus ceftriaxone
C. Azithromycin plus gentamicin
D. Ciprofloxacin
E. Spectinomycin

QUESTION#2

PREVIEW QUESTION

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?

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 10 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
- Rectal LGV (L1-L3) has made a resurgence***
- Longer duration of therapy for L1-L3 serotypes **<u>if symptomatic</u>*****
- Association with reactive arthritis (Reiter's); prompt treatment reduces risk of reactive arthritis

CHLAMYDIA TRACHOMATIS

- Serological classification
  - A,B, Ba, C (Trachoma)
  - D-K (Genitourinary and ocular infections)
  - L1-L3 (Lymphogranuloma venereum)

CHLAMYDIA TRACHOMATIS D-K

MEN

- Asymptomatic
- Urethritis
- Epididymitis (70% of cases in young men)
- Proctitis
- Conjunctivitis
- Pharyngitis (rare)
- **Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)**

WOMEN

- Asymptomatic
- Cervicitis
- Urethritis
- **Pelvic inflammatory disease**
- Bartholinitis
- Proctitis
- Conjunctivitis
- **Reactive arthritis**

CHLAMYDIA: DIAGNOSTICS

- Detection of WBCs on Gram's stain is not sensitive
- Cell culture (sensitivity 70%), direct immunofluorescence, non-amplified molecular tests (sensitivity ~85%), and NAATs (gold standard; sensitivity >95%; specificity >99%)
- FDA cleared for the detection of *C. trachomatis* on endocervical and urethral swab specimens, urine, vaginal swab specimens, throat and rectal swabs
- **Routine NAATs do NOT distinguish between D-K and L1-L3 serotypes. Multiplex tests do. The latter are not commercially available**

CHLAMYDIA TRACHOMATIS TREATMENT

- Duration of therapy depends on serotype:
  - D-K serotypes: **<u>doxycycline 100mg PO BID X 7d is preferred;</u>** alternate is 1 g oral azithromycin
  - L1-L3 serotypes (if moderate to severe proctitis): **Doxycycline 100 mg PO BID X3 weeks** (preferred); alternate is azithromycin 1g PO q week X 3 weeks
- Use of azithromycin is safe in pregnancy
- Test-of-cure (repeat testing 3–4 weeks after completing therapy) is **not** routinely recommended
- Screen all persons treated for chlamydia infection 3 months later (REINFECTION rates are high)

AZITHROMYCIN VS. DOXYCYCLINE

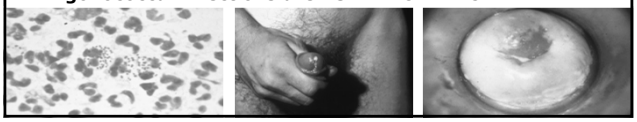
- **Urogenital** *C. trachomatis*
  - RCT in correctional facility: azithromycin=97% vs. doxycycline=100% (noninferiority of azithromycin was **not** established) Geisler NEJM 2015
- **Rectal** *C. trachomatis*
  - 2 Recent RCTs: Efficacy difference in favor of doxycycline of 20% Dombrowski CID 2021; Lau NEJM 2021

GONORRHEA: TAKE-HOME POINTS

- Drug resistance: IM ceftriaxone 500 mg is now the preferred regimen
- Pharyngeal gonorrhea: ceftriaxone is the only drug that is recommended; test of cure 7-14 days after treatment
- Disseminated gonococcal infection: patients may NOT have symptoms of urethritis
- Gonococcal conjunctivitis: 1g of ceftriaxone

NEISSERIA GONORRHOEAE

- Clinical presentation similar to that seen with *C. trachomatis*.
  - no association with Reiter's
  - responsible for 30% of cases of epididymitis in young men
  - **MOST cases (>90%) of pharyngeal and rectal gonococcal infections are ASYMPTOMATIC**



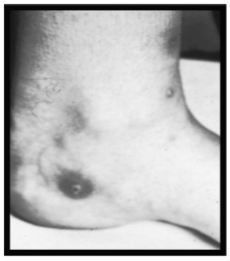
SCREENING FOR GONORRHEA

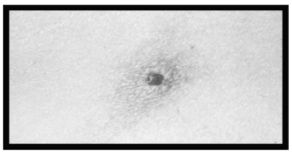
- HIV-infected men and women
- Sexually active MSM (**at all sites of exposure**)
- Individuals with new or multiple sexual partners
- Sexually active women <25
- Sexually active individuals living in areas of high *N. gonorrhoeae* prevalence
- Individuals with a history of other sexually transmitted infections
- Women ≤35 and men ≤30 in correctional facilities at intake

DISSEMINATED GONOCOCCAL INFECTION (DGI)

- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions), asymmetrical arthralgia, tenosynovitis, or (monoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause minimal genital inflammation
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE)
- Differential diagnosis: meningococcemia, RMSF, dengue, staphylococcal endocarditis, Reiter's
- Treatment: Ceftriaxone IM/IV usually 5-7 days; longer with arthritis

DGI





GONORRHEA DIAGNOSTICS

- A negative Gram's stain should NOT be considered sufficient for ruling out infection in **asymptomatic** men. In addition, Gram's stain of endocervical specimens, pharyngeal, or rectal specimens are not sufficiently sensitive or specific to detect infection
- Sensitivity of culture ~80-90% from endocervical or urethral specimens in symptomatic persons; <50% from throat/rectum
- NAATs offer the widest range of testing specimen types because they are FDA-cleared for use with endocervical swabs, **vaginal swabs**, male urethral swabs, and female and **male urine**
- NAATs are now FDA-cleared for specimens obtained from the rectum and pharynx; they are the 'tests of choice' for these sites

GONORRHEA THERAPY

- The only first-line option for uncomplicated gonorrhea is **ceftriaxone** (**500 mg** IM x1)
  - >5% of isolates in the US in 2019 had elevated MICs to azithromycin so it was abandoned as first-line therapy

St Cyr MMWR 2020

GONORRHEA THERAPY (CONT.)

- Second-line agents for **urogenital** or **rectal infections**:
  - Cefixime (800mg PO X1)
  - Gentamicin 5mg/kg IM+ 2g azithromycin
  - **Azithromycin 2g PO X1 is no longer recommended**
- **There are NO second-line recommendations for pharyngeal gonorrhea**- it's ceftriaxone or bust!
  - Gentamicin and cefixime have lower efficacy for pharyngeal infections Ross JDC, et al. *Lancet* 2019
  - All pharyngeal infections: must do a test of cure within 2 weeks after ceftriaxone therapy

St Cyr MMWR 2020

GONORRHEA THERAPY CONTINUED

- **DGI**: Ceftriaxone 1g IM or IV until clinically better (can also use cefotaxime and ceftizoxime); then, can complete 7-day course of therapy with a PO cephalosporin (once results of antibiotic susceptibility testing are available)
- **Gonococcal conjunctivitis**: Ceftriaxone 1g IM X1

EXTRAGENITAL GONORRHEA AND CHLAMYDIA

- 90% are asymptomatic
- NAATs, now FDA cleared, are the preferred (and most sensitive)diagnostic modality
- CDC recommends screening for both GC and CT at the rectum but screening for only GC at the throat
- Sexually active MSM should be screened at all sites of exposure
  - The majority of GC cases in MSM would be missed if genital-only testing were performed
- No formal extragenital screening guidelines for women

NON-GONOCOCCAL URETHRITIS (NGU)

- Gram stain of urethral secretions demonstrating ≥2 WBC per oil immersion field or positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBC per hpf
- More common etiologies:
  - *Chlamydia trachomatis* (25% cases)
  - ***Mycoplasma genitalium* (30% of cases)**
  - *Trichomonas vaginalis* (10-25% of cases; mainly MSW not MSM)
  - *Ureaplasma urealyticum* (controversial; do NOT test for this bacterium)
  - HSV
- Less common etiologies: anaeobes; enterobacteriaceae, Haemophilus, *Staphylococcus saprophyticus*, adenovirus
- NGU treatment: **doxycycline 100mg PO BID X 7d is now the preferred regimen**

NON-GONOCOCCAL URETHRITIS (NGU) CONTINUED

- If a person with NGU fails to respond to therapy, think of 4 possibilities: (1) Reinfection (2) *M. genitalium* that did not respond to above therapy (see next slide) (3) *T. vaginalis*- rare in MSM (treat with metronidazole) or (4) HSV

MYCOPLASMA GENITALIUM

- Strong association with non-gonococcal urethritis (NGU) [up to 30% of cases] and up to 35% of cases of persistent urethritis
- Moderate association with cervicitis and PID; weaker association with infertility
- Test men with persistent urethritis or epididymitis; consider testing women with persistent cervicitis or PID (discuss with patient); consider testing in men and women with persistent proctitis symptoms
- FDA-cleared diagnostic test now available
  - Combined molecular diagnostic with molecular detection of macrolide resistance is not yet FDA cleared (it is available in Europe and Australia)

M. GENITALIUM THERAPY

- Doxycycline 100mg PO BID X 7days (success rate ~30%)
- Azithromycin 1g PO X1 (success rate now <50%)
  - Azithromycin should NOT be used unless you know the organism is sensitive to the macrolides
- **Moxifloxacin 400mg POX 7-14 days is now the drug of choice**
  - Emerging resistance to fluoroquinolones (13.6% moxifloxacin resistance) Emerg Infect Dis. 2017;23(5):809-812
- Pristinamycin was highly effective in treating macrolide- and quinolone-resistant strains (not FDA approved)

Clin Infect Dis. 2015 ;60(8):1228-36

SUMMARY: URETHRITIS APPROACH

- All men presenting with urethritis should be tested for both GC and CT and treated with 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 presents complaining of a vaginal discharge.

Her examination is remarkable for a gray homogenous discharge. A vaginal swab is obtained which reveals a pH>6.0, motile trichomonads, and the presence of 3 Amsel's criteria.

QUESTION #3

Which of the following is the most appropriate antimicrobial regimen for her and her partner?

	Patient	Partner
A	Metronidazole 2g X1	None
B	Metronidazole 2g X1	Metronidazole 2g X1
C	Metronidazole 1 week	None
D	Metronidazole 1 week	Metronidazole 2g X1
E	Metronidazole 1 week	Metronidazole 1 week

TRICHOMONAS VAGINALIS

- May be asymptomatic in both men and women; causes vaginitis and NGU
- Diagnosis: culture and PCR; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: Treat all women with metronidazole 500mg PO BID X 7 days OR tinidazole 2g PO X1 [do NOT use topical gel formulations]
  - RCT: 7 days of metronidazole superior to 2g single dose Kissinger et al. Lancet Inf Dis 2019
- Therapy: Treat all men with metronidazole 2g PO X1 OR tinidazole 2g PO X1
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance (see next slide)
- Partners in the preceding 60 days must be treated
- No need to screen asymptomatic pregnant women for trichomonas; **screen all women with HIV annually**

TRICHOMONAS & NITROIMIDAZOLES

- **Tinidazole** has a longer serum half-life and achieves higher tissue concentrations than metronidazole; MICs to tinidazole lower than to metronidazole
- Can use 2g of oral tinidazole to treat both men and women
- If patient fails Rx with metronidazole & reinfection is excluded:
  - Option 1: Tinidazole 2 g PO X1
- If patients fails option 1 above:
  - Option 2: Metronidazole 2g PO QD X 5d
  - Option 3: Tinidazole 2g PO QD X 5d

BACTERIAL VAGINOSIS

- Complex polymicrobial infection; causes vaginitis (thin, white, discharge with 'fishy' odor) and cervicitis; may increase risk of PID
- May be sexually-associated but not a STD; partners do NOT need to be treated
- Dx: Nugent's score preferred in research settings; Amsel's clinical criteria performed in clinical settings:(1) discharge (2)pH>4.5 (3) clue cells (4) amine odor with KOH (whiff test)

BACTERIAL VAGINOSIS

- Rx: Metronidazole 500mg PO BID X 7days OR Clindamycin 300mg PO TID X 7 days OR topical metronidazole gel or clindamycin cream OR Secnidazole 2g PO X1 dose
  - *L crispatus* supplements after topical metronidazole resulted in a 34% reduction in recurrence at 3m Cohen NEJM 2020
- **Do NOT use metronidazole 2g PO X1**
- **BV during pregnancy:** associated with preterm labor, PROM, post-partum endometritis
- Treat all **symptomatic** cases of BV during pregnancy; **screening asymptomatic pregnant women for BV if high risk for pre-term delivery (e.g., history of premature delivery) is no longer recommended**

PELVIC INFLAMMATORY DISEASE (PID)

- Diagnostic criteria- only ONE of the following:
  - Cervical motion tenderness
  - Uterine tenderness
  - Adnexal tenderness
- Hospitalize
  - Pregnant
  - Tubo-ovarian abscess
  - Appendicitis cannot be excluded
  - Did not respond to PO antibiotics
  - Patient has nausea and vomiting, or high fevers/severe illness
  - Unreliable follow-up if treated as outpatient
- MOST patients with PID can be treated as outpatients (including first-episode PID and HIV positive women who do not meet above criteria)

PELVIC INFLAMMATORY DISEASE (PID)

- **THERAPY**
  - **Ceftriaxone** 250 mg IM in a single dose **PLUS Doxycycline** 100 mg orally twice a day for 14 days **WITH Metronidazole** 500 mg orally twice a day for 14 days
  - **Cefotetan** 2 g IV every 12 hours **OR Cefoxitin** 2 g IV every 6 hours **PLUS Doxycycline** 100 mg orally or IV every 12 hours
- Additional recommended regimens can be found in the 2021 CDC STI Treatment Guidelines (online at cdc.gov)
- All patients treated with PO regimens should improve within 3 days otherwise, admit for parenteral antibiotics
- Treat all sex partners in preceding 60 days

FITZHUGH-CURTIS SYNDROME

- Perihepatitis: RUQ pain or pleuritic pain; usually NO LFT abnormalities (or very mild)
- Complicates ~10% of PID cases
- Pathophysiology: ?Direct extension of pathogens vs. immunological mechanism
- Rx: NSAIDs (+ treat PID)

EPIDIDYMITIS

- In young men:
  - *C. trachomatis* (70%)
  - *N. gonorrhoeae* (30%)
- In older men: *E. coli* causes majority of cases
- Therapy:
  - **Ceftriaxone 500mg IM X1 + Doxycycline 100mg PO BID X 10 days**
  - For acute epididymitis most likely caused by sexually-transmitted chlamydia and gonorrhea and enteric organisms (men who practice insertive anal sex): Ceftriaxone IM X1 + levofloxacin X 10 days
  - For acute epididymitis most likely caused by enteric organisms: Levofloxacin 500mg PO X10 days

QUESTION #4 PREVIEW QUESTION

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+)

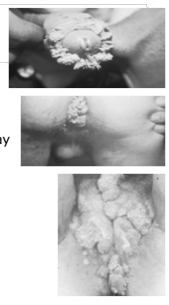
OTHER CAUSES

- 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

26 – Sexually Transmitted Infections: Other Diseases and Syndromes

Speaker: Khalil Ghanem, MD

GENITAL WARTS

- 90% of warts caused by HPV 6 & 11; concomitant infection with types 16, 18, 31, 33, and 35 increases risk of HSIL
- Genital warts may develop months or years after infection
- Up to 60% of warts will recur within 3 months after therapy. Many will clear spontaneously after 12 months
- Available therapies do not completely eradicate infectivity
- Hypopigmentation or hyperpigmentation can occur with ablative modalities (cryotherapy and electrocautery) and with immune modulating therapies (imiquimod).
- No c-section in pregnant women with visible warts
  - C-section only if the warts are obstructing the birth canal or if vaginal delivery may lead to increased risk of bleeding

HPV VACCINES

- **Nonavalent (6, 11, 16, 18, 31, 33, 45, 52, 58)**; 2-3 doses given over 6-12 months (2 doses induce good immunity if age<=14 years)
- Consists of VIRUS-LIKE PARTICLES (**noninfectious**; NO DNA)
- Efficacy: >97% against CIN 2/3, vulvar, and vaginal lesions; >98% against genital warts*
- Recommended for routine use in 9- to 26-year-old women (even those who have a history of abnormal Pap smears); routine use in boys ages 11-12 years, catch-up for males ages 13-21, and permissive use of the vaccine in men ages 22-26; vaccine FDA cleared for women up to age of 45 (but ACIP has not recommended it in women age>26)

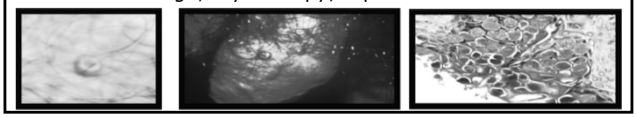
*FDA approved a supplemental biologics licensure application in 6/2020: prevention of oropharyngeal and other head and neck cancers caused by HPV types targeted by the vaccine

HPV VACCINES (CON'T.)

- Do not give during pregnancy; no need to restart schedule for patients who don't follow-up on time: JUST PICK UP WHERE YOU LEFT OFF
- Continue routine Pap smears on all women who get the vaccine
- Side effects: vasovagal response; local reactions
- Not a therapeutic vaccine

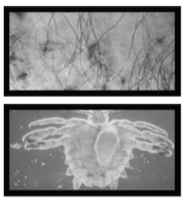
MOLLUSCUM CONTAGIOSUM

- Poxvirus
- 1 to 5mm lesions; painless papules; CENTRAL UMBILICATION
- Not necessarily sexually transmitted
- Molluscum bodies: intracytoplasmic inclusions
- Rx: curettage; cryotherapy; topical cidofovir

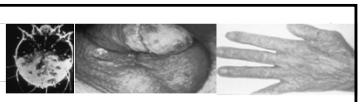


PEDICULOSIS PUBIS

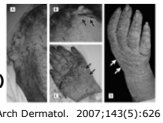
- Pediculosis pubis= pubic lice= crabs (*Pthirus pubis*)
  - Nits confined to upper shaft=old infection (no need for retreatment)
  - Maculae ceruleae (blue gray macules)
  - Permethrin 1% cream OR Pyrethrins with piperonyl butoxide (topical)
  - Resistance increasing; consider malathion 0.5% lotion or Ivermectin in case of treatment failure
  - Do NOT use Lindane; toxicities include seizures and aplastic anemia
  - Treat sex partners within previous 30 days



SCABIES



- *Sarcoptes scabei*
- Severe pruritus; especially at night or after bathing; burrows; the diagnosis is usually a clinical one
  - Permethrin cream 5% (wash off after 8 hours) OR
  - Ivermectin 200 mcg/kg PO day 1 and 14
  - Only use Lindane as an alternative
- **Crusted scabies** or 'Norwegian scabies'
  - **Mainly occurs in immunodeficient patients (HIV)**
  - **May NOT cause pruritus or burrows**
  - Contagious and aggressive
  - **Ivermectin 250mcg/kg on days 1, 15, and 29**
- Rash and pruritus of scabies may persist for up to 2 weeks after successful therapy***



Arch Dermatol. 2007;143(5):626

27

HSV and VZV in Immuno-competent and Immunocompromised Hosts

Dr. Richard Whitley

27 – HSV and VZV in Immuno-competent and Immunocompromised Hosts

Speaker: Richard Whitley, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Richard J. Whitley, MD
Co-Director, Pediatric Infectious Diseases
Children's Hospital of Alabama
Loeb Eminent Scholar Chair in Pediatrics
Distinguished Professor of Pediatrics
Professor of Microbiology, Medicine, and Neurosurgery
The University of Alabama at Birmingham

6/23/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

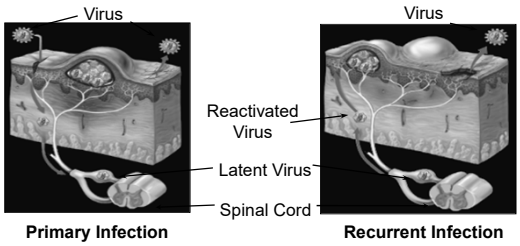
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Chairperson: NIAID COVID-19 Vaccine DSMB**
- **Chairperson: Merck Letermovir DMC and GSK IDMC for Zoster**
- **Scientific Advisory Board: Treovir, LLC**
- **Member, Board of Directors at Evrys Bio**
- **Member, Board of Directors at Virios Therapeutics**

Herpes Viruses: The Family

- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

Viral Latency and Reactivation



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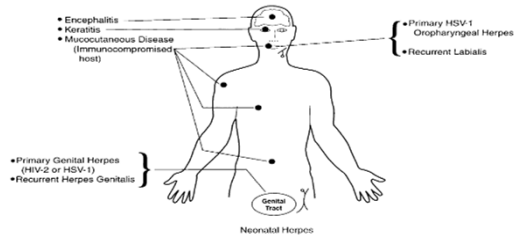
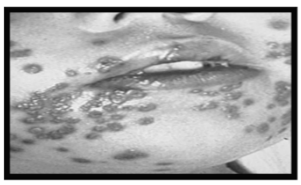
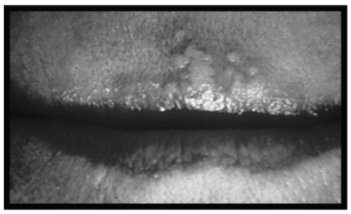
Clinical Manifestations of Herpes Simplex Virus Infections



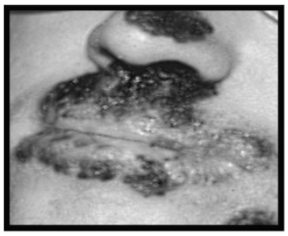
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



Herpes Simplex Labialis

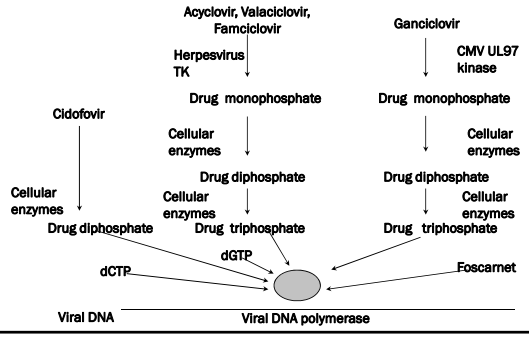


Immunocompromised Host



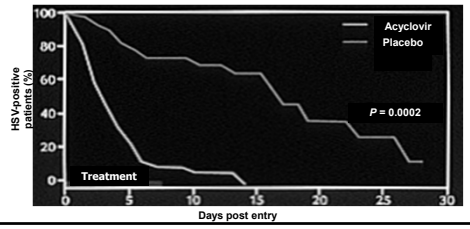
Most Widely Used Systemic Anti-HSV and VZV Drugs

- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir



Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

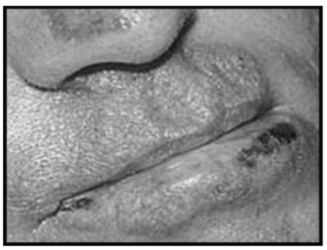
Time to cessation of viral shedding with acyclovir



Acyclovir Prophylaxis for HSV Infection in BMT Patients

Acyclovir (250 mg iv/m2 /tid) or placebo for 18 days beginning 3 days before transplant

Group	Number of Patients	Number of HSV Infections	P
Acyclovir	10	0	~0.003
Placebo	10	7	



Question #1

2022 PREVIEW QUESTION

A 30 year old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive in spite of high-dose intravenous therapy. The most likely cause for disease progression is a deficiency or alteration of:

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

Question #1b

2022 PREVIEW QUESTION

Which is the best treatment choice for this patient?

A. Give high-dose of intravenous acyclovir
B. Give intravenous ganciclovir
C. Give oral famciclovir
D. Give oral ganciclovir
E. Give intravenous foscarnet

Global Prevalence of HSV-2 Infection

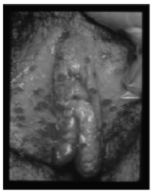
Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

Acyclovir Therapy of Genital Herpes

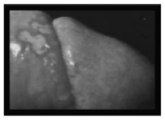
Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

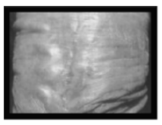
Spectrum of HSV Clinical Presentation



First infection

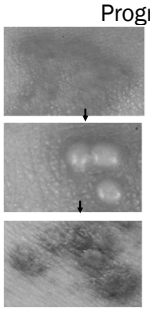


Classical recurrence



Atypical recurrence

Progression of Lesions



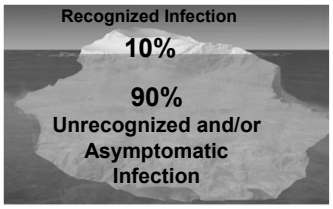
Early Redness/Swelling

Thin-Walled Fluid-Filled Vesicles and Pustules

Early Healing of Vesicles, Erosions, or Ulcers

Clinical Spectrum of HSV-2

HSV-2 Seroprevalence



Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839.

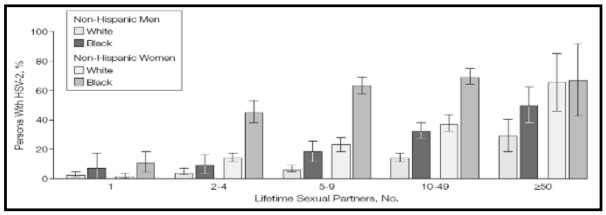
Changes in Weighted Herpes Simplex Virus 2 Seroprevalance Age 14 to 49 years

NHANES

		1988-1994		1999-2004	
	Sample Size	HSV-2 Seroprevalence (95% CI)	Sample Size	HSV-2 Seroprevalence (95% CI)	Change (95% CI)
Overall	9165	21.0	11,508	17.0	-19.0
Age Group					
14-19	1787	5.8	4650	1.6	-72.4
20-29	2750	17.2	2412	10.6	-38.4
30-39	2557	27.8	2251	22.1	-20.5
40-49	2061	26.3	2195	26.4	0

JAMA, August 23/30, 2006 Vol 296 No 8 pg 968

Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004



JAMA, August 23/30, 2006 Vol 296 No 8 pg 967

HSV-1 Genital Isolates Among U.S. College Students

Sex Transm Dis 2003;30:797-800

Genital Herpes: Transmission

Men — Asymptomatic Recurrence ⇄ Women

Transmission — Symptomatic Recurrence → 30%

Transmission → 70%

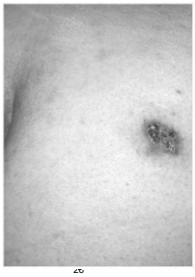
Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.

Genital Herpes: Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

Genital Herpes – A Clinician's Guide to Diagnosis and Treatment. American Medical Association. 2001:1-20.
Whitley RJ, *et al. Clin Infect Dis*. 1998;26:541-555.

Herpes Presenting as Ulceration



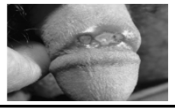
- **The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.**
- **What is the key to the diagnosis?**
  - **A. the fact that lesions recurred**
  - **B. site of involvement is not unusual**
  - **C. trauma can induce reactivation**

Photo courtesy of Jeffrey Gilbert, MD.

Question #2

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-21 2022 PREVIEW QUESTION

An 18 year old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.

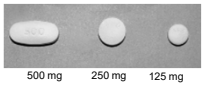


Which of the following diagnostic tests is most likely to yield the specific diagnosis?

A. Serum RPR
B. Serum FTA-Abs
C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab

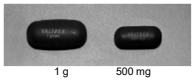
Oral Antiviral Therapies

- **Famciclovir [Famvir®]**



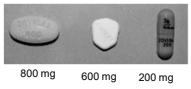
500 mg 250 mg 125 mg

- **Valaciclovir [Valtrex®]**



1 g 500 mg

- **Acyclovir [Zovirax®]**



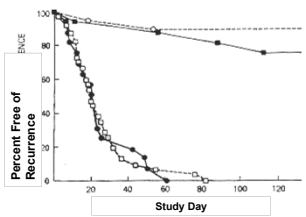
800 mg 600 mg 200 mg

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

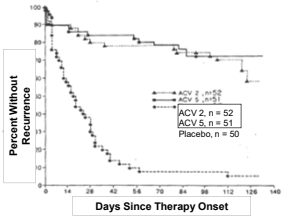
Impact of Acyclovir Therapy on Primary Genital HSV Infection

	Treatment Group (Days)			
	Acyclovir	**Placebo**	**RR**	**P**
Virus Shedding	**2.8**	**16.8**	**6.82**	**0.0002**
Pain	**8.9**	**13.1**	**2.00**	**0.01**
Scabbing	**9.3**	**13.5**	**2.21**	**0.004**
Healing	**13.7**	**20.1**	**1.83**	**0.04**

Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes



Straus, et al. *NEJM*, 1984



Douglas, et al, *NEJM*, 1984

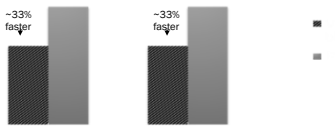
Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

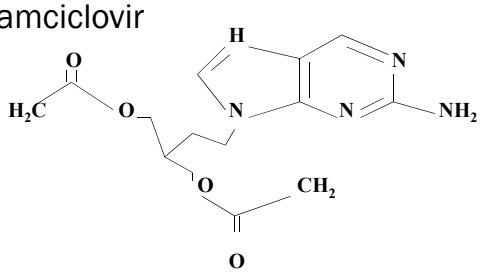
Acyclovir/Valacyclovir Kinetics

DRUG	DOSE	PHARMACOKINETICS	
		C_{max} (μg/mL)	Daily AUC (μg/mL•h)
VALTREX	1 g 3x/d	5.0	47
Oral ZOVIRAX	800 mg 5x/d	1.6	24
IV ZOVIRAX	5 mg/kg 3x/d	9.8	54
	10 mg/kg 3x/d	20.7	107

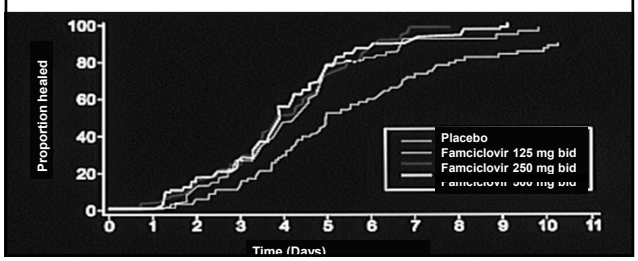
Therapy of Recurrent Genital Herpes: Duration of Disease



Famciclovir



Famciclovir Therapy of Recurrent Genital Herpes



Shorter and Shorter Therapy

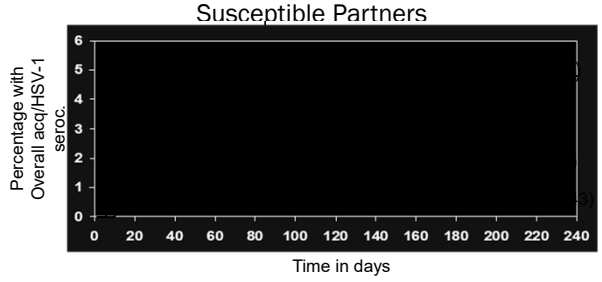
- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

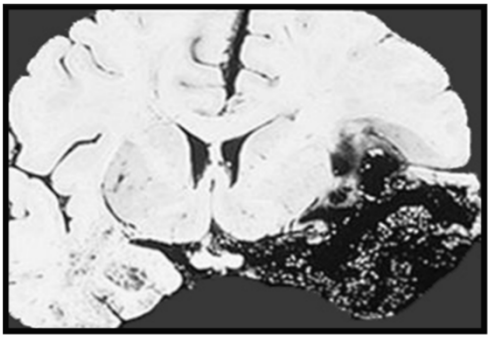
Prevention of Person to Person Transmission

Valacyclovir Prevention of HSV Transmission to Susceptible Partners

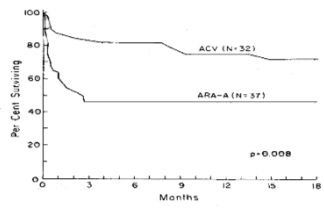
Susceptible Partner	Val-ACV N = 743	Placebo N = 741	Total
No. acquired HSV-2	14	28	42
No. acquired HSV-1	0	4	4
No. developed clinical HSV-2	4	17	21

Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners





Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A) vs Acyclovir (ACV); P=0.008

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

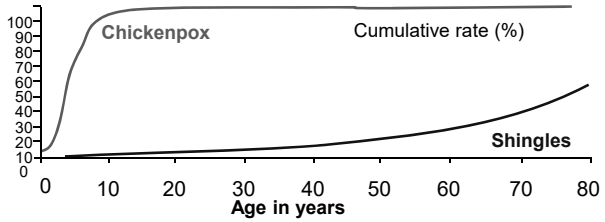
Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

Sensitivity and Specificity of PCR

	Biopsy Positive	Biopsy Negative
PCR Positive	53	3
PCR Negative	1	44

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

Varicella Zoster Virus Infection



Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

CHICKEN POX: Is Therapy of Value

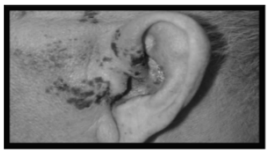
Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

	Acyclovir (n=38)	Placebo (n= 38)	*P*
Time to maximum number of skin lesions (days)	1.5	2.1	0.002
Days of new lesion information	2.7	3.3	0.03
Time to onset of cutaneous healing (days)	2.6	3.3	<0.001
Time to 100% crusting (days)	5.6	7.4	0.001
Maximum number of lesions	268	500	0.04

Thoracic Herpes Zoster

Questions

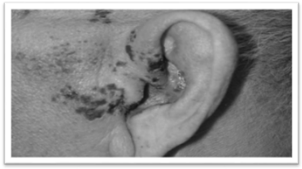
1. What is the most likely diagnosis?
2. How would you prove the etiology?



Question #3

What complication would you be most concerned about?

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies



http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

Question #4 Stem

The patient has only the observed finding on his nose.

- **What is your most likely diagnosis?**
- **What is the name of this sign?**

www.medscape.com

Question #4

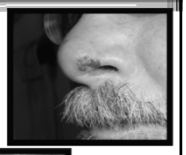
What complication is it most likely to be associated with this illness?

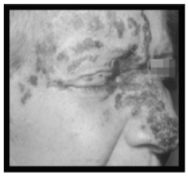
A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

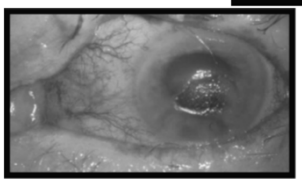
www.medscape.com

Hutchison's Sign

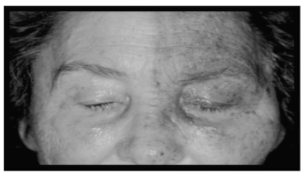
Zoster Involving nasociliary branch, Cranial Nerve VII which inervates the tip of the nose and the cornea







Zoster Ophthalmicus



NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- **Acute neuritis may precede rash by 48 - 72 hours**
- **Maculopapular eruption, followed by clusters of vesicles**
- **Unilateral dermatomal distribution**

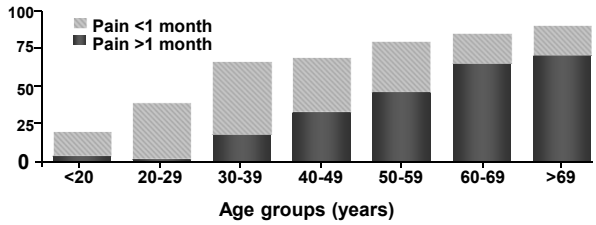
NATURAL HISTORY OF ZOSTER IN THE NORMAL HOST

- Events of healing:
  - Cessation of new vesicle formation: 3 - 5 days
  - Total pustulation: 4 - 6 days
  - Total scabbing: 7 - 10 days
  - Complete healing 2 - 4 weeks
- Cutaneous dissemination can occur dissemination is extremely rare
- Postherpetic neuralgia in 10% - 40% of cases

Complications of Zoster

Common	Uncommon
• Postherpetic neuralgia • Ocular complications • Ophthalmic zoster • (uveitis, keratitis, scleritis, optic neuritis) • Pneumonitis • Scarring • Bacterial superinfection	• Cutaneous dissemination • Herpes gangrenosum • Hepatitis • Encephalitis • Motor neuropathies • Myelitis • Hemiparesis (granulomatous CNS vasculitis)

Prevalence and Duration of Pain



de Moragas et al. *Arch Derm.* 1957;75:193-196.

Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

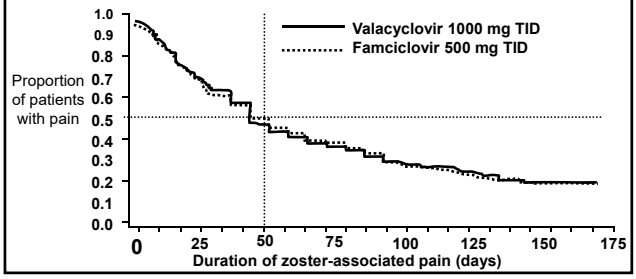
Time to Cessation of Zoster-Associated Pain

Time to Cessation of Zoster Associated Pain

n = 1141

* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

Question #5

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

Question 6

A 32 year previously healthy female is referred by an ophthalmologist for treatment of acute retinal necrosis, diagnosed in her office earlier that day. You recommend which of the following as initial therapy:

- A. sulfadiazine and pyrimethamine
- B. ganciclovir IV
- C. acylovir PO
- D. acyclovir IV
- E. foscarnet IV

METHODS OF PREVENTING / MODIFYING VARICELLA

Pre-exposure:	Oka varicella vaccine
Post-exposure:	VZIG (now available in US)
	Oka varicella vaccine (<3 days after exposure)
	Acyclovir (7-14 days after exposure)

Shingles Prevention Trial: Zostavax

- **Attenuated, live virus (approved 2006)**
- **Efficacy but waning of immunity with time**
  - **Burden Of Illness 61.1% (51.1 – 69.1%)**
  - **Post-Herpetic Neuralgia 66.5% (47.5 – 79%)**
  - **Incidence of Herpes Zoster 51.3% (44.2 – 57.6%)**

Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - Two shots
  - > 50 years of age if normal immunity; >18 yo if immunosuppressed
- **Efficacy**
  - Both PHN and incidence of shingles
  - >90% for >4 years
- **Adverse events**
  - Local reactogenicity: redness and pain ~ 50-70%
  - Systemic malaise/fever: ~30%

Thank You
rwhitley@uab.edu

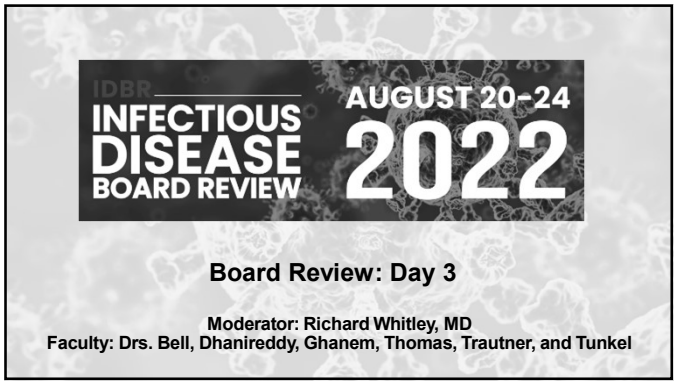
BR3

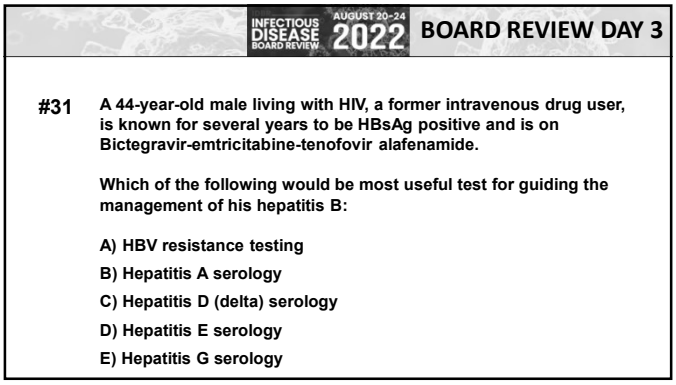
Board Review Session 3

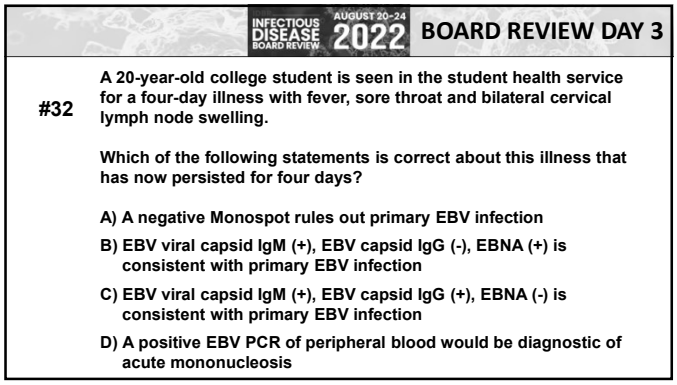
Drs. Whitley (Moderator), Bell, Dhanireddy, Ghanem, Thomas, Trautner, and Tunkel

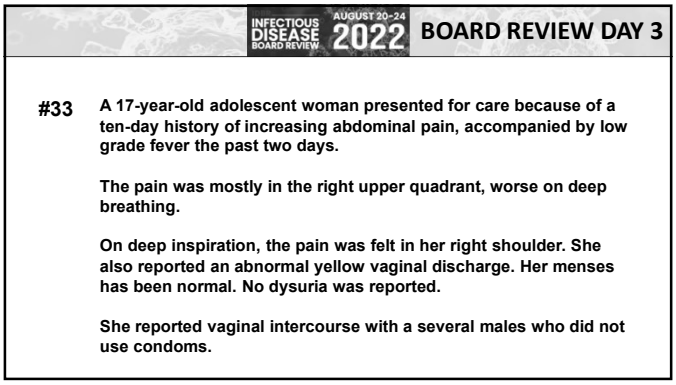
BR3 – Board Review: Day 3

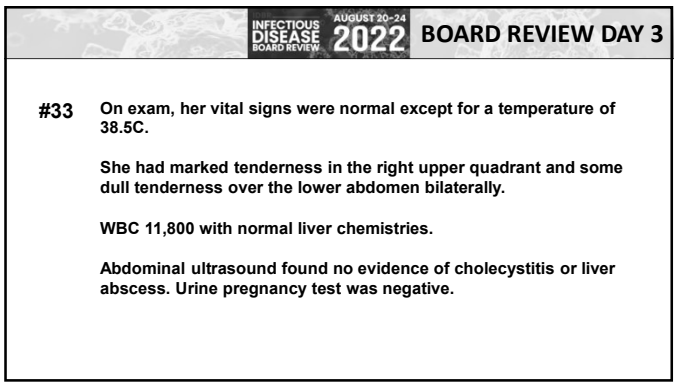
Moderator: Richard Whitley, MD

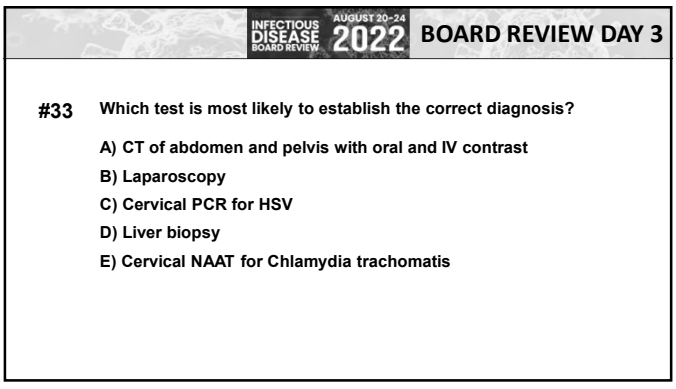












INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#34 **A 23-year-old monogamous man presents to clinic asking about the HPV vaccine.**

He states he has been in a monogamous relationship with the same man for three years.

He has no allergies and has never received an HPV vaccine.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#34 **Which of the following is correct?**

A) He is too old for the catch-up schedule for the HPV immunization of boys

B) If he is monogamous, he is at low risk for the acquisition of HPV and does not need to be immunized

C) He should begin immunization with the nine-valent vaccine

D) He should begin immunization with either the bi-valent or the nine valent vaccine

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#35 **You've been charged with leading a program to decrease ventilator-associated pneumonia (VAP) rates in the medical intensive care unit.**

You gather a multidisciplinary team with nurses, doctors, respiratory therapists, pharmacists, physical therapists, and the unit clerk.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#35 **Which of the following initiatives is most likely to lower VAP rates and improve outcomes for patients on mechanical ventilation?**

A) Begin bathing patients twice daily with povidone iodine

B) Provide oral care with 0.12% chlorhexidine solution twice daily

C) Switch to using silver coated endotracheal tubes for all patients

D) Introduce a protocol to minimize sedation and increase patient mobility

E) Put patients in the Trendelenburg position in order to encourage drainage of respiratory secretions away from the lungs

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#36 **A 72-year-old man with a history of diabetes and obesity presents to his primary care physician with a complaint of foul-smelling, cloudy urine.**

He does not have dysuria or voiding difficulties, but he reports recent loss of 10 pounds without dieting.

He has not seen a urologist or had any urinary instrumentation. No recent fevers noted, and he is afebrile at this visit.

Urinalysis shows 100 WBC/HPF and many bacteria; culture grows E. coli sensitive to trimethoprim-sulfamethoxazole. He is treated with a 7-day course of trimethoprim-sulfamethoxazole.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#36 **He returns to his primary care physician a week after completing the course of antibiotics and reports his urine is still cloudy and foul-smelling. Now he notices that his urine has bubbles towards the end of emptying his bladder. He has no other urinary symptoms.**

CBC shows anemia and mild leukocytosis. Repeat urine culture grows Proteus, sensitive to trimethoprim-sulfamethoxazole, ceftriaxone, fosfomycin and ertapenem. Stool is positive for occult blood.

His vital signs are normal on physical examination, but he is slightly pale. He does not have suprapubic tenderness.

BR3 – Board Review: Day 3

Moderator: Richard Whitley, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#36 **Which of the following is the most appropriate management?**

A) 14-day course of oral trimethoprim-sulfamethoxazole
B) IV ertapenem
C) Ultrasound of prostate
D) Abdominal/pelvic CT scan with rectal contrast
E) Oral Fosfomycin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#37 **You are asked to see a 67 yr old man who had been admitted for headache and increasing confusion over the past week.**

Earlier today he had been found to have a 4.5 cm right parietal brain abscess on CT. On that CT the right mastoid was full of fluid.

On exam, he is afebrile, unable to respond to verbal stimuli but moves all extremities. Neurological exam is otherwise unremarkable.

Optic fundi cannot be visualized because of cataracts and the right external auditory canal is blocked with cerumen.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#37 **The patient appeared to wince on pressure over the right mastoid process. You recommend urgently which of the following:**

A) Lumbar puncture
B) ENT consultation for possible otitis media
C) Neurosurgical aspiration of the abscess
D) Neurosurgical resection of the abscess
E) Trial of empirical antibiotics

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#38 **A 26-year-old cis-gender man develops mild burning on urination without any significant discharge. He is tested by Nucleic Acid Amplification Testing (NAAT) of his urine and is negative for gonorrhea and Chlamydia.**

Several urethral discharge samples evaluated by wet mount preparations demonstrate > 5 WBCs/HPF but no organisms were observed on Gram's staining.

His male partner is asymptomatic and had negative gonorrhea and chlamydia testing.

The patient has no other symptoms and feels well otherwise. An HLA B-27 histocompatibility antigen is negative.

One course of treatment with doxycycline has been unsuccessful.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#38 **A likely cause of this patient's complaints is:**

A) Chlamydia trachomatis
B) Neisseria gonorrhea
C) Trichomonas vaginalis
D) Mycoplasma genitalium
E) Reiter's Syndrome (reactive arthritis)

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 **BOARD REVIEW DAY 3**

#39 **A 37-year-old female nurse comes to your office to get advice. She recently spent four weeks on a mission trip in Chad, and one week prior to coming back to the United States she received a minor bite on her lower leg from a stray dog.**

She cleaned the wound and took a few days of amoxicillin/clavulanic acid.

Efforts to obtain rabies vaccine and rabies immune globulin in Chad were unsuccessful.

The wound healed without complication and she is feeling well.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#39 She had a tetanus shot last year.

When she was a child living overseas she had serum sickness after receiving horse tetanus immune globulin.

She has been back in the United States for a week, so it has been two weeks since she had the bite and the site is not inflamed.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#39 What treatment is indicated?

A) Nothing else is indicated at this late date

B) Rabies vaccination only

C) Rabies immune globulin in the buttocks and rabies vaccination

D) Rabies immune globulin in the bite site and rabies vaccination

E) Rabies vaccine and skin testing for allergy to horse serum prior to administration of rabies immune globulin

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#40 A 66-year-old man comes to the Emergency Room with severe nausea and vomiting for 6 hours with diarrhea for 2 hours.

He has been in relatively good health but has adult-onset diabetes, mild congestive heart failure, and hypercholesterolemia.

He has no history of prior GI problems and no one else in his family is ill, including the two toddlers that his wife cares for in his home. On physical examination, he is febrile to 38.3°C, BP 150/80, RR 20, P 100.

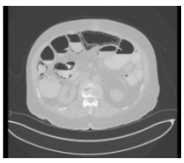
He has a mildly tender abdomen with no rebound.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#40 Laboratory:

- WBC 11,000 (60% polys), Hg 13 g/dl, Plat 220,000
- Chemistry Profile: Na 145 meq/L, K 3.8 meq/L, CO2 22 meq/L, BUN 20 mg/dl, Creat 2.0 mg/dl, Lactate 0.9 mmol/L
- Stool cultures sent: rotavirus screen negative

CT Scan:



The ER starts vancomycin and ciprofloxacin plus metronidazole and calls you for a consultation.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#40 What is the appropriate response to the finding of pneumatosis intestinalis in this patient?

A) Immediate laparotomy

B) Change antibiotic regimen to meropenem and vancomycin

C) Add caspofungin to ciprofloxacin and metronidazole

D) Colonoscopy

E) Observation of clinical course: no change in current management

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#41 A 19-year-old female in her 10th week of pregnancy was seen in the obstetrics clinic for routine follow-up when the history was elicited that she had taken care of her friend's child all day three days prior and that child had now developed chickenpox.

The patient was a recent immigrant from rural Nigeria, had no recollection of chickenpox or shingles and no knowledge that she had ever been immunized or exposed to chickenpox previously.

The OB clinic has called to see if anything should be given as post-exposure prophylaxis.

You cannot obtain a varicella titer for at least 3 more days since this call comes…Friday afternoon.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

#41 Your advice is which of the following:

A) Nothing
B) Chickenpox vaccine
C) Varicella zoster immune globulin
D) Varicella zoster immune globulin plus chickenpox vaccine
E) Intravenous immune globulin (IVIG)

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

#42 A 28-year-old woman just finished a course of glecaprevir and pibrentasvir for chronic HCV infection.

12 weeks after finishing this guideline recommended course, her HCV RNA is negative.

She was F0 on elastography pre-treatment and her post-treatment liver function tests are normal.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

#42 Which counseling is most relevant to this patient:

A) Avoid all alcohol use
B) Avoid statins or other drugs that cause hepatotoxicity
C) Avoid needle sharing or unprotected sex with HCV infected persons
D) Avoid pregnancy for 24 months to eliminate the risk of perinatal transmission from the HCV that was treated
E) Avoid ibuprofen

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

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

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

Admission blood cultures have grown MSSA.

Nafcillin and a TTE have been ordered.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

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

On your examination, temperature is 39C, pulse 120 and BP 160/90.

The patient is alert but has severe back pain.

He is unable to walk because of pain but has weakness in both legs and absent deep tendon reflexes in both legs.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022 BOARD REVIEW DAY 3

#43 The next thing that should be done is which of the following:

A) Surgical decompression of the spinal cord
B) Aspiration of the epidural abscess by interventional radiology
C) Nafcillin is sufficient for the present
D) Add rifampin to nafcillin
E) High dose dexamethasone

BR3 – Board Review: Day 3

Moderator: Richard Whitley, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#44 A 25-year-old graduate student is seen for penile ulcers. The ulcers have been present for two weeks and are painful. He says the ulcers began as "red bumps" that developed into "pimples" and then eroded into ulcers.

Over the past 2-3 days he noted a tender lump in his groin.

The problem began during a trip to Africa from which he returned just three days ago. While in Africa he had vaginal intercourse with several commercial sex workers while he was inebriated and did not always use a condom.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#44 On exam he is afebrile and findings are confined to his genital area.

There are two 1cm adjacent "kissing" ulcers in the coronal sulcus. They are tender and filled with a yellow purulent exudate.

There is a tender, large lymph node in the left groin.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#44 Which one of the following is the most likely cause of his problem?

A) Treponema pallidum

B) Herpes simplex

C) Chlamydia trachomatis

D) Haemophilus ducreyi

E) Klebsiella (Calymmatobacterium) granulomatis

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#45 A 46-year-old man with poorly controlled diabetes presented with fever and acute onset of urinary retention.

In the emergency room, a urinalysis was sent, which revealed 55 WBC/HPF, 10 RBC/HPF. Urine culture, unfortunately, was not performed.

He was diagnosed with UTI and sent home with an indwelling Foley catheter and 10 days of ciprofloxacin. A follow-up visit with urology was requested but was not scheduled to occur until 2 months later.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#45 One month after his ER visit, he came to the clinic to see his regular physician. The urinary catheter was still in place.

He reported feeling hot/sweaty with shaking chills for the past 2 nights, and he also reported new back pain. His measured temperature in the clinic was 104°F.

On examination, he had left-sided costovertebral angle tenderness.

He was admitted to the hospital and started on ciprofloxacin. The urinary catheter was removed, and his post-void residual volume was <100 cc of urine.

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20–24 2022 BOARD REVIEW DAY 3

#45 His admission urine culture grew Klebsiella pneumoniae and Serratia marcescens.

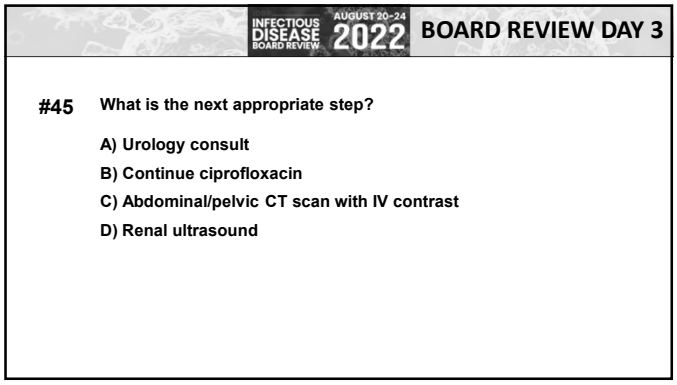
His admission blood culture (one set) grew Serratia marcescens in both bottles. Both organisms were sensitive to ciprofloxacin.

On hospital day 3, his maximum temperature was 101°F, and he developed right testicular pain/swelling.

Examination revealed a tender mass in the posterior aspect of the right scrotum, with overlying erythema. Scrotal ultrasound revealed right epididymitis.

BR3 – Board Review: Day 3

Moderator: Richard Whitley, MD



28

Syndromes in the ICU that ID Physicians Should Know

Dr. Taison Bell

28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Syndromes in the ICU that Infectious Disease Physicians Should Know

Taison D. Bell, MD, MBA
Assistant Professor of Medicine, UVA School of Medicine
Division of Pulmonary and Critical Care Medicine
Division of Infectious Disease and International Health

7/18/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Question 1: What proportion of patients in the ICU develop fever during their stay?

A. Less then 5%

B. Between 15-25%

C. Over 50%

D. Everyone. Absolutely everyone

Exam Blueprint: Critical Care Topics ~8-10%

Critical care medicine	General internal medicine
Systemic inflammatory response syndrome (SIRS) and sepsis	Malignancies
Ventilator-associated pneumonias	Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome)
Noninfectious pneumonias (eosinophilic and acute respiratory distress syndrome [ARDS])	Noninfectious inflammatory disorders (e.g., vasculitis, lupus, inflammatory bowel disease)
Bacterial pneumonias	Dermatologic disorders
Viral pneumonias	Hematologic disorders
Hyperthermia and hypothermia	Noninfectious central nervous system disease
Near-drowning and *Scedosporium* and *Pseudallescheria* infection	Bites, stings, and toxins
	Drug fever
	Ethical and legal decision making

Question 2

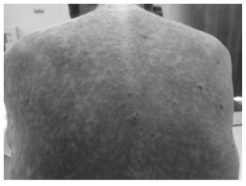
IDBR 2022 PREVIEW QUESTION

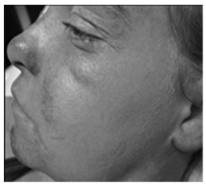
- **You are asked to see a 35 year-old woman with a history of seizure disorder admitted to the ICU with a fever to 40°C, hypotension, and a maculopapular rash**
- **She is being empirically treated with vancomycin and piperacillin-tazobactam. Blood, urine, and sputum cultures (taken prior to antibiotic initiation) are negative**
- **Exam: Tachycardia with otherwise normal vital signs. Diffuse maculopapular rash with facial edema and sparing of the mucosal surfaces**
- **Labs are notable for elevated AST/ALT and peripheral eosinophilia**
- **Only home medication is lamotrigine, which was started two weeks prior to admission**

Her clinical syndrome is most consistent with:

A. Sepsis
B. Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
C. DRESS (drug-induced hypersensitivity syndrome)
D. Erythema Multiforme
E. Neuroleptic Malignant Syndrome (NMS)

Morbilliform Rash with Facial Edema and Eosinophilia





28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

DRESS (drug-induced hypersensitivity syndrome)

Rash Characteristics	Morbilliform involving >50% BSA, inflamed, facial edema, infrequent mucosal involvement
Onset	Usually 1-3 (up to 6) weeks after drug exposure
Other Features	Fever, LAD, other organ involvement in 80% (liver, kidney, pancreas, heart, lung), expansion of CD4/8 T cells → Herpesviridae reactivation (HHV6)
Lab Findings	Eosinophilia, lymphocytosis/lymphopenia, atypical lymphocytes
Classic Meds	Aromatic AEDs (highest with lamotrigine), Vancomycin, Raltegravir, Dapsone and other Sulfas, anti-TB RIPE
DDx	SLE, mycoplasma, viral hepatitis, mononucleosis
Treatment	Withhold offending agent, supportive care Steroids, CsA, IVIg are controversial. Mortality is high

Exanthematous drug eruptions

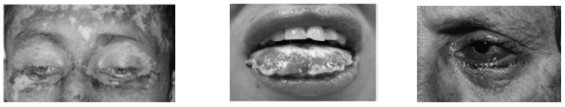
- T-cell-mediated, delayed type IV hypersensitivity reaction
- Diffuse maculopapular rash (morbilliform)
- Highest incidence with aromatic antiseizure medications: carbamazepine, phenytoin, and lamotrigine (1:100)

SJS/TEN	AGEP	DRESS
• Severe blistering • Mucosal involvement common • SJS: <10% BSA • TEN: >30% BSA	• Rapidly spreading (hours) pustular lesions • Mucosal involvement rare • Common ddx: psoriasis	• > 50% BSA • Facial edema • Infrequent mucosal involvement • Eosinophilia

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Rash Characteristics	Erosive mucositis of oral, urogenital, and ocular sites SJS: <10% BSA; TEN: >30% BSA
Onset	4-28 days after drug exposure
Other Features	Fever, partial or full thickness injury with painful necrolysis, pulmonary and GI manifestations
Lab Findings	Leukopenia, no eosinophilia
Risk Factors	Aromatic AEDs, infection (mycoplasma), GVHD, HIV
Treatment	Withhold offending agent, supportive care Steroids and IVIg are controversial

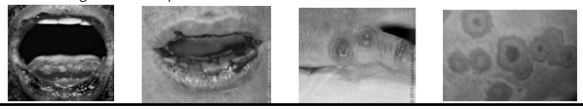
Stevens Johnson and Toxic Epidermonecrolysis



- "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
    - Others

Erythema Multiforme

- Immune mediated
- Distinctive target lesions that are usually asymptomatic
  - Febrile prodrome in some cases
- Often associated with oral, ocular, and genital mucosal lesions
- Less severe than DRESS or SJS or TEN
- Causes: Infection > Drugs
  - Infections: HSV, Mycoplasma, many others
  - Cancer, autoimmune, drugs, etc
- Self Limiting in 10-14 days



Extreme Hyperpyrexia (T>41.5C)

- Heat Stroke
  - Exertional (football player in August)
  - Non-exertional (Elderly)
  - Lack of hydration and/or inability to sweat
- Drugs
  - Cocaine, ecstasy etc.
- The Pyrexic Syndromes

28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

Question 3

- You are called to the PACU to see a 29-year-old previously healthy male with a fever of 41.6℃ who is 4 hours 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?:

A. Antihistamines
B. High-dose corticosteroids
C. Dantrolene
D. IVIG
E. Dilantin

Malignant Hyperthermia

- Syndrome - Rare (~700 cases/year) but 5-10% mortality
  - Muscle contraction (masseter spasm)
  - Cardiovascular instability
  - Steep rise in CO2
- Genetic defect
  - Ca++ transport in skeletal muscle
  - Autosomal dominant
    - (excessive calcium accumulation)
- Triggers
  - Usually < 1 hour after trigger (up to 10 hours)
  - Classic: Halothane, succinylcholine

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
    - (direct muscle relaxant for up to 10 days)
  - Dopamine agonists (bromocriptine and others)

www.nmsis.org, 1-888-667-8367

Serotonin Syndrome

Clinical Characteristics of Serotonin Syndrome	
Pathogenesis	Excess Serotoninergic Activity • Therapeutic drugs, drug interactions, self poisoning
Triggers	• Linezolid = MAO Inhibitor • SSRI inhibitors (Bupropion) • Antiemetics (Granisetron) • Tricyclic antidepressants (amitriptyline)
Clinical Manifestations	• Acute onset (within 24 hrs of new drug/drug change) • Hyper-reflexive>bradyreflexia • Nausea, vomiting, diarrhea, tremors followed by shivering
Treatment	• Withdraw offending medication • Consider benzodiazepines and cyproheptadine

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	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, myoglobinemia	Nothing classic

Hypothermia: <35℃

- Causative Drugs
  - Beta blockers (metoprolol)
  - Alpha blockers (clonidine)
  - Opioids
  - Ethanol
  - Antidepressants
  - Antipsychotics
  - Aspirin
  - Oral hypoglycemics
- Syndrome
  - Hypotension due to fluid shifts
  - *Give broad spectrum antibiotics empirically if they fail to raise temperature 0.67C/hour
  - Consider adrenal or thyroid insufficiency
- Treatment
  - Rewarming
  - "ABC"s
    - Airway, Breathing, Circulation

Question 4

- You are called to the medical ICU to see a 47 y/o woman with a history of alcoholic cirrhosis with ARDS and shock
- Initially admitted to general medicine for encephalopathy in the setting of skipping lactulose doses
- On HD#3 developed ARDS, thought to be from aspiration
- Subsequently goes into distributive shock. Started on vancomycin and piperacillin-tazobactam
- Patient has daily fevers to 39°C and a persistent low-dose levophed requirement
- Labs: mild hyponatremia and hyperkalemia. Metabolic acidosis
- Micro: blood, urine, sputum, and ascitic fluid are benign
- Radiology: CXR with unchanged b/l multifocal opacities, RUQ USG benign, Abd CT benign

Which of the following would you give?:

A. Broader spectrum antibacterial treatment
B. Stress dose corticosteroids
C. Dantrolene
D. IVIG
E. Antifungal therapy

Differential Diagnosis of Shock

Ohm's Law

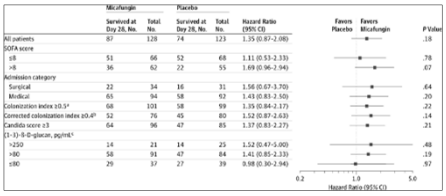
MAP = CO x SVR

Cardiogenic (flow)
- MI/CHF/Tamponade
- PE
- Tension PTX
- Hypovolemia

Distributive (resistance)
- Sepsis
- Toxic shock syndrome
- Aspiration
- Anaphylaxis
- Neurogenic
- Adrenal insufficiency

Why not empiric antifungal? EMPIRICUS

Muti-center RCT of 260 Adults in ICU
- Non-neutropenic
- Multiorgan failure
- ICU-acquired sepsis
- On MV at least 5d
- At least 4d broad spectrum Abx in prior week
- Multifocal candida colonization



JAMA. 2016;316(15):1555-1564

Question 5

A patient with end stage renal disease on dialysis through a tunneled hemodialysis catheter is admitted to the medical ICU with altered mental status, hypotension, and fever. On exam he has obvious purulence at the catheter site.

For the patient's syndrome, which of the following is NOT an evidence-based intervention?

A. Early and effective antibiotics
B. Albumin as the preferred resuscitation fluid
C. Measuring serum lactate
D. Fluid resuscitation with 30 cc's/kg crystalloid

FYI: Sepsis 3 Definition: Not Testable!

- Definition of Sepsis
  - "Life-threatening organ dysfunction due to a dysregulated host response to infection"
- Definition of Septic Shock: Sepsis
  - Absence of hypovolemia
  - Vasopressor to maintain mean blood pressure >65mmg
  - Lactate >2 mmol/L (>18 mg/dL)
- Predicting Outcome
  - Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
  - Quick Sofa is relatively specific but not very sensitive

Sepsis 3 Definition: For Background (Not Testable)!

	Traditional Definition	Sepsis 3
Sepsis	Suspected or known infection with ≥ 2 SIRS criteria	Life-threatening organ dysfunction due to a dysregulated host response to infection - SOFA score ≥2 points or positive qSOFA
Severe Sepsis	Sepsis + organ failure	N/A
Septic Shock	Severe sepsis + hypotension refractory to adequate fluid resuscitation or addition of vasopressors	Sepsis with adequate resuscitation with vasopressor requirement and lactate ≥ 2 mmol/L

Increase in the Sequential Organ Failure Assessment (SOFA) score (10% mortality)
Quick Sofa is relatively specific but not very sensitive

28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

Managing Sepsis

What's the Bottom Line?

- Some recommendations are plausible
  - Fluid resuscitation with 30 cc's/kg crystalloid
  - Vasopressors for MAP goal 65
    - But do not use Dopamine!

- Some are wrong
  - Early goal directed therapy
  - Tight glucose control. Better outcomes <180

- Two are unequivocally true
  - Early effective antibiotics
  - Source control

Other Things

Stress-dose steroids: conflicting data

- CORTICUS/ADRENAL
  - No change in mortality with hydrocortisone
  - **Quicker reversal of shock**
- Annane/APROCCHSS
  - Improved mortality with hydrocort/fludricort
  - **Quicker reversal of shock**

Antiendotoxin and Anticytokine therapy

- No benefit

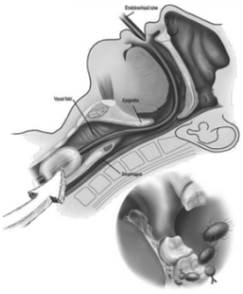
Antithrombosis (Activated Protein C)

- Taken off the market

Surviving Sepsis Campaign Bundles

3 Hour Bundle	6 Hour Bundle
- Measure lactate level - Draw blood cultures - Administer broad spectrum antibiotics - Administer 30 cc/kg IV crystalloid	- Start vasopressors if MAP <65 despite fluid resuscitation - Reassess volume status if hypotension persists after fluid resuscitation or if initial lactate ≥ mmol/L

Ventilator Associated Pneumonia



Institute for Healthcare Improvement Ventilator Care Bundle Components

- Head of bed elevation to 45°
- Daily awakening trials and assessment of extubation readiness
- Chlorhexidine oral care
- Stress ulcer and DVT prophylaxis

www.IHI.org/topics/VAP
O'Grady. JAMA 2012
Weavind. Curr. Anesth 2013

Ventilator Associated Pneumonia National Healthcare Safety Network

Pathogen	% of Isolates
Staph aureus	24.7%
Pseudomonas aeruginosa	16.5%
Klebsiella	10%
Enterobacter	8.%
E. Coli	5%

28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

IDSA VAP Treatment Guidelines

Cover for S. aureus, P. aeruginosa, and other GNRs in ALL patients (strong recommendation, very low-quality evidence)

Clinical Question	Recommendation
MRSA coverage	Use vancomycin or linezolid
PsA and other GNRs	Pip-tazo, Cefepime, Ceftazidime, Levofloxacin
Double GNR coverage?	Only if >10% of isolates are resistant to the primary abx
Double coverage agent	FQs, aminoglycosides (no monotherapy), polymyxins
Procalcitonin	Do not use for diagnosis. Consider to aid in discontinuation
Duration of therapy	7 days, consider longer or shorter based on clinical signs

Clin Infect Dis 2016; 63: e61-e111

Question

34 year-old woman with opiate use disorder is admitted to the medical ICU for acute respiratory distress syndrome requiring intubation. She has been receiving intravenous daptomycin through a PICC for tricuspid valve endocarditis for the past three weeks. Transthoracic echo is unchanged from prior and chest CT shows bilateral ground glass opacities with scattered areas of consolidation. Blood cultures are negative. Bronchial alveolar lavage shows a predominance of eosinophils with negative cultures.

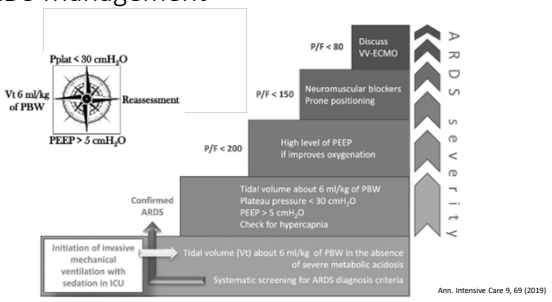
Which of the following is the most likely cause of her respiratory illness?

A. Injection drug use
B. Septic pulmonary emboli
C. Daptomycin
D. Sepsis

Eosinophilic Pneumonia

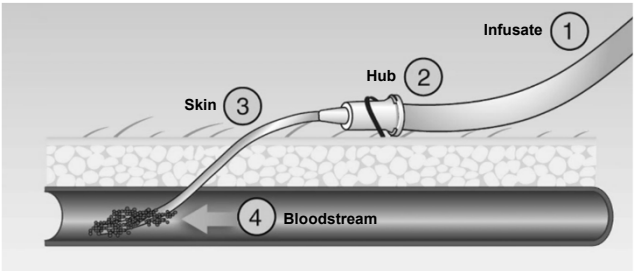
- Rare disorder characterized by eosinophil infiltration of the pulmonary parenchyma
- Often associated with peripheral eosinophilia
- Many drugs linked: daptomycin, nitrofurantoin, amiodarone, ACE-i's, etc.
- Daptomycin-induced EP: precise mechanism unknown but believed to be related to daptomycin binding to pulmonary surfactant leading to epithelial injury

ARDS Management



Ann. Intensive Care 9, 69 (2019)

CLABSI



Antiseptic Techniques: Catheter Insertion

Hand Hygiene	• Soap & water or alcohol-based rub before/after insertion (IB) • Sterile gloves while inserting (IA)
Skin Prep	• Chlorhexidine solution before insertion and during dressing changes (IA) • Allow to fully dry before insertion (IB)
Barrier	• Maximum barrier protection: cap, mask, sterile gown, sterile gloves and full sterile drape (IB)

CID 2011:52 (1 May)

28 – Syndromes in the ICU that Physicians Should Know

Speaker: Taison Bell, MD

Remove the Catheter

- On the Board Exam
  - It's almost never wrong to remove/replace catheter
- Syndromes Requiring Removal
  - Septic shock
  - Septic thrombophlebitis/Venous obstruction
  - Endocarditis
  - Positive blood cultures>72 hrs after appropriate abx
- Organisms Requiring Removal
  - Staph aureus
  - Atypical mycobacteria
  - Candida species
  - Proprionibacteria
  - Pseudomonas aerug
  - Bacillus species
  - Malssezia
  - Micrococcus

Antibiotic Impregnated Catheters and Hubs Plus Antibiotic Lock Solutions

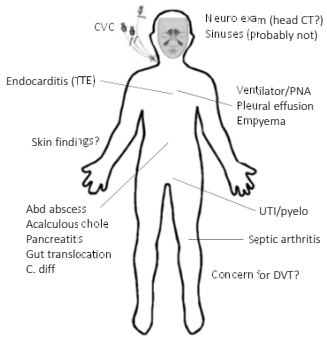
- Not likely testable on the boards
- They have a role, but not well defined

Near Drowning/Submersion Injuries

- Prophylactic Antibiotics
  - Not indicated unless water grossly contaminated
  - Steroids not indicated
- Etiologic Agents
  - Water borne organisms common
    - Pseudomonas, Proteus, Aeromonas
- Therapy for Pneumonia
  - Directed at identified pathogens

Approach

- Run med list
- Consider AI
- Pyrexic syndromes



Thank You

- Good luck!
- Please give feedback
- Contact
  - taison.bell@virginia.edu
  - Twitter: @TaisonBell

29

Immunizations: Domestic, Travel, and Occupational

Dr. Shireesha Dhanireddy

29 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Immunizations:
Domestic, Travel, and Occupational

Shireesha Dhanireddy, MD
Professor, Allergy & Infectious Diseases
University of Washington

7/7/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

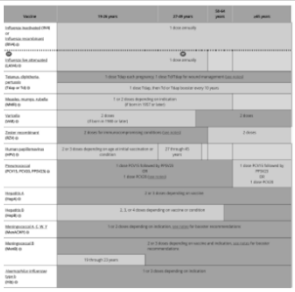
- **None**

Objectives

- Review vaccine guideline resources
- Review ACIP recommendations for routine immunizations
- Discuss travel immunizations
- Review vaccines in special populations

Key Sources

Only ACIP guidance for routine immunizations will be tested



https://www.cdc.gov/vaccines/schedules/hcp/adult.html

Key Sources

Only CDC guidance from yellow book for travel vaccines will tested

https://wwwnc.cdc.gov/travel/page/yellowbook-home

Egg Allergy

22 year old man with h/o egg allergy and no prior influenza vaccine presents for routine visit. He states he has had hives after eating eggs. No h/o anaphylaxis. **Which of the following is recommended?**

A. Defer vaccination and refer to an allergist for testing
B. Vaccinate with any inactivated influenza vaccine without monitoring
C. Vaccinate and monitor for 30 minutes after receiving any inactivated influenza vaccine
D. Vaccinate with only live attenuated influenza vaccine

Egg Allergy – ACIP Recommendations

- Egg allergy
  - 1.3% of children
  - 0.2% of adults
- Ok to get influenza vaccine if the following:
  - No reaction with cooked eggs
  - Only hives after exposure
- If have anaphylaxis, angioedema, respiratory distress or required epinephrine
  - CAN STILL RECEIVE VACCINE – but should be given by a provider who can recognize allergic reactions
  - 33 cases of anaphylaxis out of 25.1 million doses
  - 8/33 had symptoms within 30 min

Question: Measles Vaccine

71 year old man underwent unrelated HSCT for MDS AML 12 years ago which was relatively uncomplicated without GVHD and he has been off immunosuppression for 2 years. His primary care provider checks a rubeola serology as there is an outbreak in the community and patient is concerned regarding risk. The serology is negative.

Which of the following do you recommend?

A. Vaccine is not recommended as it is live and there is risk of vaccine related disease
B. One dose of MMR vaccine recommended
C. Two doses of MMR vaccine recommended

Measles Vaccine

Who doesn't need vaccine:

- Adults born before 1957 (except HCW – should receive during an outbreak)
- Those with laboratory evidence of immunity

Who needs 1 dose:

- Adults born after 1957 considered low risk without documented vaccine and no lab evidence of immunity or prior infection

Who needs 2 doses:

- Healthcare workers
- International travelers born in 1957 or later
- Persons attending colleges or post-high school educational institutions

Measles Vaccine

Measles vaccine may be administered post-transplant if:

- 2 years post transplant
- No active GVHD
- At least 1 year off immunosuppressive medications

Question: HPV Vaccine

A 24 year old healthy male presents for routine clinic visit. He is not on any medications. He smokes cigarettes. He is sexually active with both men and women and uses condoms consistently. Which of the following is correct regarding HPV vaccine?

A. He should receive 2 doses of HPV-9 spaced 6 months apart
B. He should receive 3 doses of HPV-9 at 0, 1, and 6 months
C. He does not need HPV vaccine as he is already sexually active
D. HPV vaccination is only recommended in males through age 21

HPV Vaccine

As of late 2016, only the nonavalent (9vHPV) vaccine is being distributed in the US

Nonavalent: Merck Gardasil 9®
- Types 6, 11, 16, 18, 31, 33, 45, 52, 58
- FDA-approved for females and males **9-45*** yrs
- Cost per dose $133-$193

HPV Vaccine Recommendations

- Routine vaccination at age 11 or 12 years*
- Recommended for everyone through age 26 if not previously vaccinated
- **Vaccine not recommend for everyone older than 26 years**

BUT

- **May consider for ages 27 through 45 through shared decision making**

* Vaccination series may be started at 9 years of age

MMWR 2019;68:698-702

Now 2 Doses Adequate in Some Populations

- For boys and girls age 9-14:
  - –2 dose schedule: 0, 6-12 months
- For those who are >14 or immunocompromised:
  - –3 dose schedule: 0, 1-2, 6 months
  - –2 dose schedule not yet tested in this group, stay tuned
- Hope to reduce costs and increase uptake!

Meites et al, MMWR 2016: 65(49); 1405-1408.
Iversen et al, JAMA 2016: 316(22); 2411-2421.

2022 PREVIEW QUESTION

Question: Pneumococcal Vaccine

A 37 year old man recently diagnosed with HIV presents to clinic for routine care after starting antiretroviral therapy 3 months ago. He has not received pneumococcal vaccination.

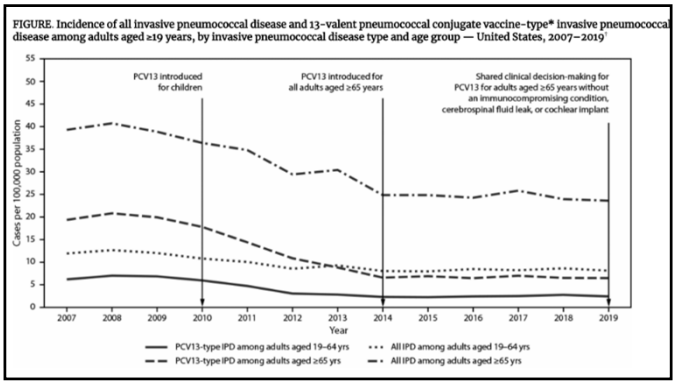
Which of the following is most accurate?

A. He does not need pneumococcal vaccination as he is under 65
B. He needs a PCV13 alone
C. He needs a PCV13 followed 1 year later by a PPSV23
D. He needs a PCV20 alone

Pneumococcal Disease

Age (years)	Disease Incidence Cases/100,000 (number of cases)	Death Rate Deaths/100,000 (number of deaths)
<1	17.7 (702)	0.20 (8)
1	12.6 (500)	0.20 (8)
2–4	5.07 (606)	0.13 (16)
5–17	1.23. (659)	0.00 (0)
18–34	2.33 (1,757)	0.08 (60)
35–49	6.48 (3,982)	0.46 (284)
50–64	14.8 (9,326)	1.47 (932)
65–74	18.0 (4,952)	2.17 (597)
75–84	29.0 (4,042)	4.53 (631)
≥85	45.4 (2,856)	11.4 (718)
Total	9.14 (29,382)	1.01 (3,254)

Gierke R et al. CDC Vaccine Preventable Diseases Surveillance Manual



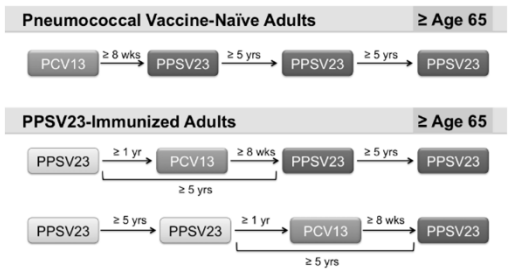
Updated Guidelines January 2022

- CDC ACIP recommended PCV20 or PCV15 to all individuals ≥ 65 years who have not received PCV before or if unknown
- For PWH, individuals with asplenia and others at increased risk, Give PCV20 or PCV15 at age 19-64
  - If PCV15 given, then give PPSV23

Pneumococcal Vaccine in Adults: Who needs it?

- Persons ≥ 65 years of age
- Persons age 19-64 with:
  - Chronic lung disease (asthma or COPD)
  - Chronic heart disease (except HTN)
  - Chronic liver disease
  - CSF leak
  - Smokers
  - Diabetes
  - Alcoholism
  - Functional or anatomic asplenia
  - Immunocompromising conditions

Pneumococcal Vaccine Schedule in People with HIV



Question: Hepatitis B Vaccine

A 35 year old woman with recently diagnosed HIV now on ART with VL UD and CD4 count 650 presents for f/u. She is HBV non-immune (HBsAb negative, HBcAb negative, HBsAg negative). She completes 3 doses of standard-dose HBV vaccine. Which of the following is most accurate?

A. She needs an additional dose of vaccine as she has HIV
B. She should have received double-dose vaccine as she has HIV
C. You should check HBsAb 1-2 months after completion, and give additional dose of vaccine if remains non-immune

ACIP Recommendations for HBV Immunization in PWH

- Recombivax® 10 mcg/mL or Engerix® 20 mcg/mL : 3 dose series (0, 1, 6 months) 10 µg/mL IM

OR

- Heplisav®: 2-dose series (0, 1 month) 20 µg in 0.5 mL IM

Anti-HBs should be assessed 1-2 months after completion of series. If anti-HBs < 10mIU/mL, then considered non-responder

2022 PREVIEW QUESTION

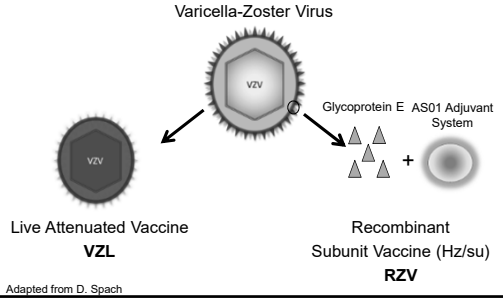
Question: Zoster Vaccine

A 62 year old woman with a self-reported history of shingles 10 years ago and type II diabetes presents to clinic. She received the live-attenuated zoster vaccine (ZVL) 2 years ago.

What do you recommend regarding the zoster vaccine?

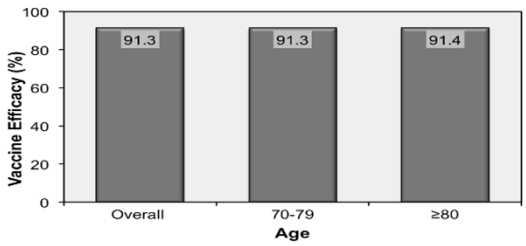
A. Vaccine not indicated given her history of zoster
B. Vaccine not indicated as she has received ZVL
C. Check VZV titer to confirm history. If negative, proceed with vaccination
D. Recommend recombinant zoster vaccine

Zoster Vaccines



Adapted from D. Spach

RZV Efficacy Against First Episode of Zoster in Immunocompetent Patients ≥50



Cunningham AL, et al. N Eng J Med. 2016;375:1019-32.

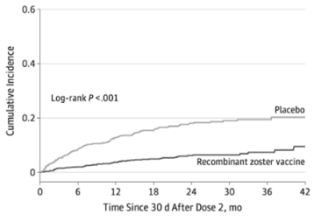
ACIP Recommendations for Zoster Vaccine

- ZVL is no longer available
- RZV is preferred over ZVL
- Healthy adults ≥ 50 years
  - Regardless of prior h/o HZ
  - No need to wait any specific period of time after HZ to give RZV (just not during acute episode)
- 2 doses, 2-6 months apart
- Wait a minimum of 8 weeks after giving ZVL to give RZV

ACIP Recommendations for Zoster Vaccine in Immunocompromised Persons

- RZV now recommended for all IC adults 18+
- 2 doses 8 weeks apart

Efficacy of RZV in Preventing Incident Herpes Zoster in Patients Who Had Undergone HSCT



Source: Bastidas et al. JAMA 2019.

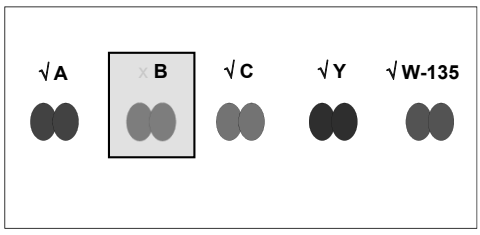
Question: Meningococcal Vaccine

44 year old woman hospitalized with anemia and thrombocytopenia diagnosed with complement-mediated HUS. Treatment with eculizumab is being considered. She is told she will need vaccine(s) prior to initiation of therapy.

A. Give meningococcal quadrivalent conjugate vaccine
B. Give meningococcal B vaccine only
C. Give both quadrivalent conjugate and meningococcal B vaccines

Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

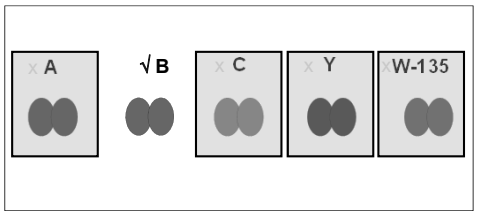


Meningococcal Quadrivalent Vaccines

Serogroups Included in Vaccine: A, C, Y, W-135

- *Menactra* (MenACWY-D)
  - Conjugate vaccine
  - Approved for ages 9 months to 55 years
- *Menveo* (MenACWY-CRM)
  - Conjugate vaccine
  - Approved for ages 2 to 55 years
- *MenQuadFi* (MenACWY-TT)
  - Polysaccharide tetanus toxoid conjugate vaccine
  - Approved for ages 2 to 55 years

Meningococcal B Vaccines



Meningococcal Group B Vaccines
Serogroups Included in Vaccine: B

- MenB-4C (*Bexsero*)
  - Recombinant vaccine
  - For ages 10 to 25 years
  - 2 dose series ≥1 month apart
- MenB-FHbp (*Trumenba*)
  - Recombinant vaccine
  - For ages 10 to 25 years
  - Healthy adolescents and young adults: 2 doses at 0, 6 months
  - Adults at risk for meningococcal disease: 3 doses at 0, 1-2, 6 months
  - Vaccinated during serogroup B meningococcal disease outbreaks: 3 doses at 0, 1-2, 6 months

ACIP Meningococcal B Vaccine Recommendation Adolescents and Young Adults

- Recommended fo
  increased risk, pr
  - Meningococcal
  - Asplenia
  - Complement d
  - On eculizumab
  - Microbiologist
    Neisseria meni
- Same vaccine should be used for all doses

Meningococcus returns to OSU: Student being treated for disease

CDC. MMWR. 2015;64:1171-6.

Eculizumab

- Soliris (eculizumab) 1000-2000x increased risk of meningococcal meningitis
- CDC recommendations –
  - –Immunize with both quadrivalent and B vaccines at least 2 weeks prior to giving eculizumab if possible
  - –Repeat immunization every 5 years while on eculizumab
- Risk remains increased despite vaccination

Question: Tdap

A 27 year old pregnant woman presents for her routine obstetrics visit at her 32 week gestation visit. She is G2P1. She has a healthy 2 year old daughter at home. Which statement is correct regarding Tdap in pregnancy?

A. She should receive a Tdap today only if she has not received in the past 5 years.
B. She should receive Tdap only if she did not receive during her prior pregnancy
C. She should receive Tdap today

Tdap Recommendations

WHO

- All adolescents aged 11 through 18 years (age 11-12 preferred)
- All adults aged 19 through 64 who have not received a dose
- All adults aged ≥ 65 years (2/2012)
- All pregnant women during each pregnancy

WHAT

- Boostrix preferred for adults ≥ 65 years (but either okay)

WHEN

- Regardless of interval between last Td if has not received Tdap
- During each pregnancy for pregnant women – optimum timing is 3rd trimester (27-34 weeks)

MMWR 2013;62:131-135

Question: Hepatitis A

A couple in their 30's plans to adopt a 2 year old girl from Ethiopia. They have a regular babysitter and another 7 year old child.

Who should receive the Hepatitis A vaccine?

A. Both parents
B. Mother only
C. Both parents and 7 year old child
D. Both parents, 7 year old child, and babysitter

Hepatitis A

- Vaccine recommended for all close personal contacts, including regular babysitters of children adopted from high/intermediate endemic areas
- Timing – ideally at ***least 2 weeks prior to arrival*** of child but within first 60 days of arrival

Hepatitis A

Hepatitis A

- Universal vaccination for children since 2006 (between 12-23 months)
- 3 formulations of vaccine available – Havrix, Vaqta, Twinrix (with Hep B vaccine)
  - Havrix and Vaqta are 2 doses 0, and 6-12 months apart
- Duration of protection is unknown but felt to be lifelong
  - No need to check antibody titers after vaccination
  - Negative titer does not mean lack of immunity

Hepatitis A Vaccination in Adults

- Travelers
- Men who have sex with men
- Persons who use illicit drugs
- Persons who work with nonhuman primates
- Persons who anticipate close contact with an international adoptee
- Persons with chronic liver disease
- Post-exposure prophylaxis for healthy persons
- **Persons living homeless**

Question: Travel

27 year old female aid worker for a relief organization is planning a 2 month trip to Nigeria in May. She recently completed graduate school. Prior travel to Brazil for vacation 11 years ago. Vaccine history - received all childhood vaccines and yellow fever vaccine 11 years ago. She should receive the following vaccines:

A. Yellow fever, Hep A, Typhoid, meningococcal, Japanese encephalitis, cholera
B. Hep A, Typhoid, meningococcal, cholera
C. Hep A, Typhoid
D. Yellow fever, Hep A

Yellow Fever

Yellow Fever Vaccine

- Recommended for ≥ 9 months traveling to or living in areas of risk or countries requiring vaccine for entry
- In 2014, WHO concluded that single dose fellow fever vaccine provides lifelong protection and no booster needed
  - Exceptions if ongoing risk and the following
    - pregnant when initially vaccinated
    - underwent HSCT after initial vaccine
    - HIV+

Yellow Fever Vaccine

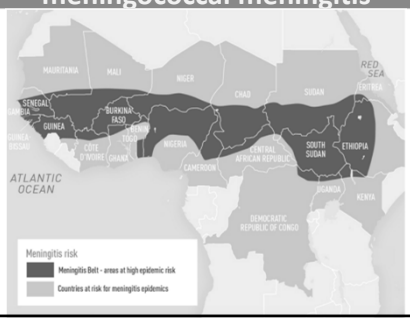
As of April 5, 2021, Yellow Fever Vaccine (YF-VAX®) is available again in US

STAMARIL® (through Expanded Access Program) no longer being shipped to US as of May 6, 2021

29 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Areas of frequent epidemics of meningococcal meningitis



Meningococcal Vaccine and Travel

- Quadrivalent meningococcal vaccine recommended for travelers to the meningitis belt during dry season (Dec-June)
  - For ages 2 months – 55 years --> MenACWY (conjugate vaccine) recommended
  - For ≥ 56 years who have received conjugate vaccine before, Men ACWY recommended
  - For ≥ 56 years who are vaccine naïve, then MPSV4 (polysaccharide vaccine) recommended
- Meningitis B vaccine not recommended for travel
- Approx 7-10 days after vaccine for the development of protective antibody levels

Meningococcal Vaccine and Travel for Umrah or Hajj

- Travelers to Saudi Arabia for Umrah or Hajj are required to provide documentation of meningococcal vaccination at least 10 days before arrival
  - –No more than 3 years before for polysaccharide vaccine
  - –No more than 9 years before for conjugate

Typhoid Vaccine

- Highest risk for travelers to South Asia (6-30 x more than other destinations)
- Increased risk in West Africa, particularly in rural areas
- 2 vaccines available in US
  - Oral, live attenuated (given at least 1 wk before travel); age 6 and above, q 5 years if ongoing risk or travel
  - IM, polysaccharide (given at least 2 wks before travel); age 2 and above, q 2 years if ongoing risk or travel
  - Both 50-80% effective
- Indicated in travelers
- Delay vaccine >72 hrs after antibacterial medications

Japanese Encephalitis

JEV

- 35,000-50,000 cases/year
- 20-30% mortality
- 30-50% with neurologic sequelae
- Very low risk in travelers *(< 1 case per million travelers)*
- Risks are extended travel > 1 month, rural areas, irrigated areas (rice paddies), or going to an outbreak area
- Vaccine 2 doses, 28 days apart. 2nd dose should be given at least a week prior to travel
- 2 months or older
  - Smaller dose for children under 3
  - ? Booster dose for ≥ 17 years if risk and > 1 year since prior vaccine

29 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

Cholera Vaccine

- Approved in 2016
- Single-dose vaccine recommended for adults 18-64 years travelling to an area of active transmission (where cases have been reported in the past year)
- Cholera in travelers is extremely rare
- Risk factors: aid workers in outbreak settings
- Vaccine 90% effective in preventing severe diarrhea (declined to 80% after 3 months)

Polio

- Decreased over 99% since 1988 (350,000 cases)

www.polioeradication.org

Polio Vaccine

One dose after age 18 years in addition to the pediatric series of 4 doses if going to area with polio

Question: Travel

A 30 year old male is planning on traveling to Angola. He presents to a travel clinic prior to travel and receives appropriate vaccines. One week later, he develops fever, ataxia, confusion, and then seizure.

Which vaccine is most likely responsible for this clinical syndrome?

A. Typhoid vaccine
B. Pneumococcal vaccine
C. Yellow fever vaccine
D. Japanese encephalitis vaccine
E. Malaria vaccine

Yellow Fever Vaccine

- YEL-AND (yellow fever vaccine associated neurologic disease)
  - Can dx by amplification of vaccine-type virus from CSF
- YEL-AVD (yellow fever vaccine associated viscerotropic disease)
  - Fever, N/V, malaise, myalgia, dyspnea
  - Jaundice, renal/hepatic impairment, rhabdo, decreased platelets, respiratory distress, hypotension, DIC
  - Diagnosis - isolate virus from blood

Vaccines Post-Exposure

Question: Rabies

A 25 year old spelunker was bitten by a bat 6 days ago. He has never received rabies vaccine in the past.

What do you recommend?

A. Observation as too late to benefit from immunization or immune globulin
B. He should receive HRIG + vaccine today, then in 3, 7, and 14 days (total 4 doses).
C. He should receive HRIG + vaccine today, and day 14 as he is already a week past exposure
D. He should receive HRIG + vaccine today, then in 3, 7, 14, and 28 days (total 5 doses)

Question: Rabies vaccine in previously vaccinated patient

A 25 year old spelunker was bitten by a bat 6 days ago. *He received rabies vaccine series 5 years ago*.

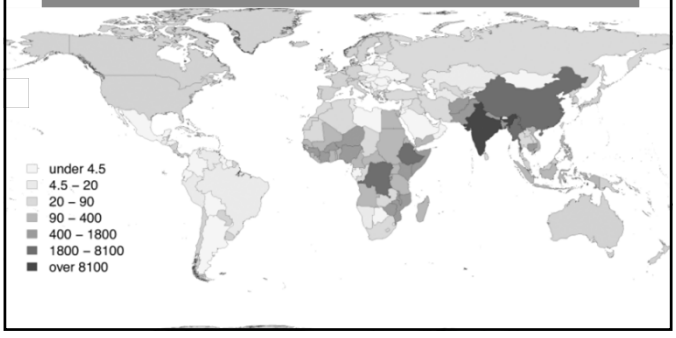
What do you recommend?

A. He does not need HRIG or additional vaccine
B. He does not need HRIG, but should receive vaccine today and in 3 days
C. He should receive HRIG + vaccine today in 3 days
D. He should receive HRIG + vaccine today, then in 3, 7, and 14 days

Rabies

- Nearly uniformly fatal disease, acute, progressive encephalomyelitis
- Incubation period 1-3 months, but can be days to years
- 1-2 cases/year in US since 1960
- No cases in 2020 and 2021
- **5 cases in US so far in 2022**

Human Deaths Attributed to Rabies, 2017



Rabies Vaccine

- Pre-exposure prophylaxis – updated February 2021
  - Vaccination on day 0, 7, ~~and 21 OR 28 days~~

Risk Category	Nature of Risk	Typical Population	Preexposure Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Bite, nonbite, or aerosol exposure.	Rabies diagnostic lab workers, spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-epizootic areas.	No vaccination necessary.

May also give booster dose between 21 days and 3 years of completing 2-dose series

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: Post-Exposure

A 50 year old man living homeless is notified by public health that 2 people living in his tent community were diagnosed with hepatitis A in the last week. He does not know if he has been vaccinated but he is not in routine medical care. He denies any symptoms. Which of the following is most appropriate:

A. He does not need vaccine as he is asymptomatic
B. He should receive Hep A vaccine as soon as possible
C. He should receive combination Hep A and Hep B vaccine as he is likely non-immune to both

Hepatitis A Post-Exposure Prophylaxis

- No PEP needed if healthy and previously vaccinated
- PEP should be given immediately (within 14 days of exposure)
- No data available for combination HepA/HepB vaccine for PEP in HAV outbreak setting (contains only half the Hep A antigen compared to HAV vaccine – so not recommended after exposure)
- If non-immune, should complete 2-dose vaccine series (2nd dose at least 6 months after 1st dose)
- Immune globulin + vaccine (at separate sites) for immunocompromised and those with chronic liver disease
- For infants < 12 months, immune globulin only ASAP (within 2 weeks)

Vaccines Post-Exposure

- ***Varicella exposure***
  - If no evidence of immunity and no contraindications (ie not severely immunocompromised) → Give vaccine ideally 3-5 days after exposure
  - For non-immune immunocompromised hosts and pregnant women, passive immunization with VariZIG is recommended
- ***Hepatitis B exposure***
  - If unvaccinated or incompletely vaccinated, Hep B vaccine dose + HBIG (can be given at a different injection site) as soon as possible after exposure
- ***Meningococcal exposure***
  - Chemoprophylaxis for close contacts (household members, child-care personnel, persons directly exposed to oral secretions)
  - Vaccination of population in outbreak

29 – Immunizations: Domestic, Travel, and Occupational-I, II

Speaker: Shireesha Dhanireddy, MD

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

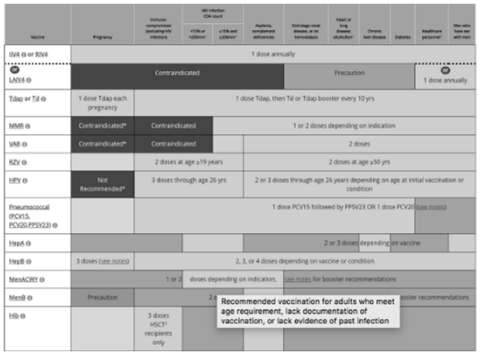
Precautions for use in:

•Individuals with latex allergy

•H/o anthrax

•Immunocompromised individuals

•Moderate to severe illness from anthrax



Vaccinations for Immunocompromised Hosts: Levels of Immunosuppression

- ***High-level Immunosuppression***
  - Combined primary immunodeficiency disorder
  - Receiving cancer chemotherapy
  - Within 2 months after SOT
  - HIV with CD4 count < 200 in adolescents/adults and < 15% in children
  - Daily steroid therapy ≥ 20mg (or > 2mg/kg/day for pts < 10kg) of prednisone or equivalent for ≥ 14 days
  - Certain biologic immune modulators or rituximab
  - HSCT (duration of high level immunosuppression variable)
- ***Low-level immunosuppression***
  - Asymptomatic HIV with CD4 count 200-499 for adolescents/adults and 15-24% in children
  - Lower doses of steroids
  - MTX ≤ 0.4mg/kg/week, azathioprine ≤ 3mg/kg/day, 6-mercaptopurine ≤ 1.5mg/kg/day

Vaccinations for Persons with HIV

<u>If CD4 count > 200</u>

Inactivated influenza

Tdap

Pneumococcal

Meningococcal

HBV

HPV

MMR

Varicella

<u>If CD4 count < 200</u>

Inactivated influenza

Tdap

Pneumococcal

Meningococcal

HBV

HPV

~~MMR~~

~~Varicella~~

Vaccinations for Persons with HIV

•Meningococcal vaccine

– 0, 8 weeks; then q5 years thereafter

•Pneumococcal vaccine age 19-64

– PCV13 once, then PPSV23 at least 8 weeks later

– Repeat PPSV23 5 years later

•No recommendations for zoster vaccine

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)
  - PCV13 once as adult, followed by PPSV23 at least 8 weeks later; repeat PPSV23 5 years later
- Above vaccines should be given at least 2 weeks prior to elective splenectomy, if possible

Vaccinations for Healthcare Workers

25 year old nursing student is being seen in student health clinic for routine visit. She brings medical records indicating that she received her first dose of hepatitis B vaccine 18 months ago and the second vaccine 1 month thereafter. She asks today if she requires additional doses. No other medical problems and she is not on any other medications.

Which of the following is most appropriate?

A. No additional doses of HBV vaccination needed
B. Restart HBV vaccine series
C. Check hepatitis B surface Ab titer to assess immunity
D. Give 3rd dose of HBV vaccine series today

Vaccines for Healthcare Workers

- Hepatitis B
  - –Pre-vaccine serologies not indicated unless born in geographic regions with prevalence ≥ 2%, MSM, PWID, immunosuppressed, liver disease NOS
  - –All HCP should be vaccinated with at least 3 doses
  - –Should have post-vaccination anti-HBs ≥ 10 mIU/mL (drawn 1-2 months after last dose of vaccine)

Post-Vaccine HBV serologies

- Serologic testing not necessary after routine vaccination of infants, children, or adults
- Anti-HBs recommended for the following:
  - – Infants born to HBsAg–positive or unknown mothers (check HBsAb and sAg)
  - – Health care personnel and public safety workers
  - – Hemodialysis patients
  - – Persons with HIV
  - – Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
  - – Sex partners of HBsAg-positive persons

Vaccines for Healthcare Workers

Hepatitis B	If you don't have documented evidence of a complete hepB vaccine series, or if you don't have an up-to-date blood test that shows you are immune to hepatitis B (i.e., no serologic evidence of immunity or prior vaccination) then you should • Get the 3-dose series (dose #1 now, #2 in 1 month, #3 approximately 5 months after #2). • Get anti-HBs serologic tested 1–2 months after dose #3.
Flu (Influenza)	Get 1 dose of influenza vaccine annually.
MMR (Measles, Mumps, & Rubella)	If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to measles or mumps (i.e., no serologic evidence of immunity or prior vaccination), get 2 doses of MMR (1 dose now and the 2nd dose at least 28 days later). If you were born in 1957 or later and have not had the MMR vaccine, or if you don't have an up-to-date blood test that shows you are immune to rubella, only 1 dose of MMR is recommended. However, you may end up receiving 2 doses, because the rubella component is in the combination vaccine with measles and mumps. For HCWs born before 1957, see the MMR ACIP vaccine recommendations.
Varicella (Chickenpox)	If you have not had chickenpox (varicella), if you haven't had varicella vaccine, or if you don't have an up-to-date blood test that shows you are immune to varicella (i.e., no serologic evidence of immunity or prior vaccination) get 2 doses of varicella vaccine, 4 weeks apart.
Tdap (Tetanus, Diphtheria, Pertussis)	Get a one-time dose of Tdap as soon as possible if you have not received Tdap previously (regardless of when previous dose of Td was received). Get Td boosters every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.
Meningococcal	Those who are routinely exposed to isolates of *N. meningitidis* should get one dose.

Resources

- www.cdc.gov/vaccines/recs/ACIP/default.htm
- www.immunize.org/acip

THANK YOU

sdhanir@uw.edu

30

Acute Hepatitis

David Thomas, MD

30 – Acute Hepatitis

Speaker: David Thomas, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Acute Hepatitis

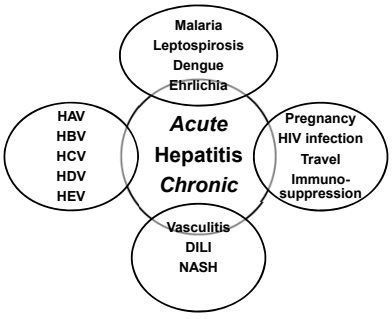
David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

7/10/2022

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck and Excision Bio



18 year-old with jaundice

- 18 y/o presents with 5d of headache, fever, diarrhea, vomiting, chest pain
- PMH – Open fractures of all R metatarsals with pins x 3mo
- SH – home tattoos; lives with parents and pregnant girlfriend; dogs and rats; swam in freshwater dam 1 wk before symptom onset; cuts grass; multiple tick bites; Maryland

Courtesy E Prochaska, MD

18 year-old with jaundice, con't

- T 39.4; BP 118/62 (then on pressors); P 91; 97% RA
- Icteric, non-injected, no murmurs
- Diffuse petechial rash; purple macules on ankle
- WBC 11,740 (92.4 P, 0.8B, 2% L); Hb 14.2; Plt 47,000
- Creatinine 0.9-3.4; CRP 10.1; Tbili 4.1 (direct 3.7); ALT/AST 26/53; CK 887
- HIV Ab neg; SARS-CoV-2 PCR neg; Monospot - neg

Courtesy E Prochaska, MD

18 year old with jaundice

The cause of his illness is:

A. Acute hepatitis A
B. Babesia microti
C. Tularemia
D. Leptospira icterohaemorrhagiae
E. HSV

Courtesy E Prochaska, MD

30 – Acute Hepatitis

Speaker: David Thomas, MD

Leptospirosis

1. **Exposure to fresh water (eg rafting in Hawaii/Costa Rico or triathlon) OR rats (Baltimore)**

Leptospirosis

2. **Bilirubin fold change > ALT**

Leptospirosis

3. **Biphasic possible and systemic findings** (conjunctival suffusion, kidney, skin, muscle, lungs, liver)

   ddx: liver and muscle: flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie, vasculitis

Leptospirosis

4. **Diagnosis:**
   - **PCR most useful (urine pos longer)**
   - **serology late**

2022 PREVIEW QUESTION

Acute Hepatitis in Uganda

- 42 year old female has malaise and RUQ pain; she just returned from 2 months working at an IDP camp in north Uganda. She endorses tick and other 'bug' bites and swam in the Nile. 1st HAV vaccine 2 days before departure. Prior HBV vaccine series.
- Exam shows no fever, vitals are normal. RUQ tender. Mild icteric. ALT 1245 IU/ml; Hb 13.4 g/dl; TB 3.2 mg/dl; WBC 3.2k nl differential.

2022 PREVIEW QUESTION

Acute hepatitis in Uganda

Which test result is most likely positive?

A. Ebola PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis "liver" antigen
E. 16S RNA for Rickettsial organism

30 – Acute Hepatitis

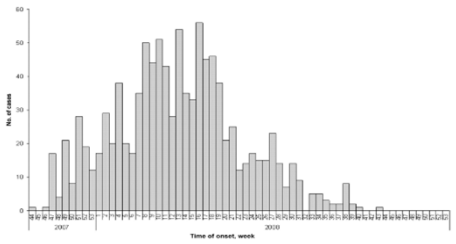
Speaker: David Thomas, MD

1. Vaccination works vs immune globulin to prevent hepatitis A *up to 14d after* exposure

End Points	Per-Protocol Population		Modified Intention-to-Treat Population†	
	Vaccine Group (N=568)	Immune Globulin Group (N=522)	Vaccine Group (N=740)	Immune Globulin Group (N=674)
	number (percent)			
Clinical				
Primary				
Any symptom plus IgM-positive and ALT ≥ twice ULN	25 (4.4)	17 (3.3)	26 (3.5)	18 (2.7)
Secondary				
Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡	29 (5.1)	19 (3.6)	30 (4.1)	20 (3.0)
Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR	18 (3.2)	12 (2.3)	19 (2.6)	12 (1.8)

Victor NEJM 2007

2. There are HEV outbreaks, eg. North-Ugandan IDP Camp



Teshale CID 2010

3. Hepatitis E: Epidemiologic Clues

- –Outbreaks – contaminated water in Asia/Africa
- –Sporadic - undercooked meat (BOAR, deer, etc)
- –Overseas travel typical
- –USA: endemic rare, genotype 3, IgG serology positive far more than can be explained by cases - can be hard to interpret

4. Hepatitis E: Clinical Clues

- –Fatalities in pregnant women
- –Can be chronic in transplant (rarely in HIV)
- –GBS and neurologic manifestations (vs other hep viruses); pancreatitis
- –Diagnosis: RNA PCR; IgM anti-HEV
- –Treatment: ribavirin for chronic

Acute Hepatitis at ID Week

- 42 year old homeless male approaches a group of ID fellows while attending ID Week in San Diego.
- One fellow noticed jaundice and suggested he seek medical testing. With what diagnosis was the fellow most concerned?

Acute hepatitis at ID week

Fellow worried about?

A. HAV
B. HBV
C. Delta
D. HCV
E. HEV

30 – Acute Hepatitis

Speaker: David Thomas, MD

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Foods

Homelessness and Hepatitis A—San Diego County, 2016–2018

Corey M. Peak,[1,2,3] Sarah S. Stous,[2] Jessica M. Healy,[4] Megan G. Hofmeister,[1] Yulin Lin,[5] Sumathi Ramachandran,[5] Monique A. Foster,[2] Annie Kao,[2] and Eric C. McDonald[2]

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]County of San Diego Health and Human Services Agency; and [3]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, San Diego, California; and Divisions of [4]Foodborne, Waterborne, and Environmental Diseases; and [5]Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Morbidity and Mortality Weekly Report (*MMWR*)

CDC > MMWR

Notes from the Field: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

Weekly / September 22, 2017 / 66(37);999-1000

1. Hepatitis A: Key Epidemiologic Clues – People, Places and Foods

Multistate Outbreak of Hepatitis A Linked to Frozen Strawberries – Current Case Count Map and Table

State	Case Count
Arkansas	1
California	1
Maryland	12
New York	5
North Carolina	4
Oregon	1
Virginia	109
West Virginia	2
Wisconsin	3
Grand Total	148

Case Count as of December 13, 2016

tropical CAFE

Outbreak of hepatitis A in Hawaii linked to raw scallops

Outbreak

2. Hepatitis A: Key Clinical Clues

- There are outbreaks all over the world
- The most common cause of acute hepatitis in USA
- Clinical syndrome
  - –fulminant on HCV
  - –relapsing: symptoms/jaundice recur <12 mo

3. Vaccination to Prevent Hepatitis A

- *Pre-exposure:* vaccinate
  - HOW: Inactivated vaccines USA (HAVRIX,VAQTA)(TWINRIX)
  - WHOM: HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/HIV pos/adoptee exposure
  - All children 1-18 yrs receive hepatitis A vaccine (since 2006)
- *Post-exposure:* vaccinate (and possibly IG)
  - Unless > 40 years or immunosuppressed then IG is 'preferred'
  - Close exposure (sex or IDU partner) not casual (eg office worker)

Victor NEJM 2007; MMWR July 3 2020; MMWR October 19, 2007 / 56(41);1080-1084

Acute Viral Hepatitis B Clues

- Most linked to sex, drugs, nosocomial
  - –Nosocomial (fingerstick devices, etc)
  - –Most transmissible (HBV>HCV>HIV)
- Clinical
  - –Acute immune complex disease possible
  - –Diagnose: IgM anti-core, HBsAg and HBV DNA
  - –New infection vs reactivation (both can be IgM pos)

More on HBV

- See lecture on chronic hepatitis for prevention, HIV coinfection, and treatment

30 – Acute Hepatitis

Speaker: David Thomas, MD

Acute Viral Hepatitis Delta will be with HBV

- **HDV**
  - –**HBV coinfection**
    - **Fulminant with acute HBV**
  - –**HBV superinfection**
    - **Acute hepatitis in someone with chronic HBV**
  - –**Test for HDV RNA**

Acute Viral Hepatitis C clues

- **HCV**
  - –**IDU link (hepatitis in Appalachia)**
  - –**HIV pos MSM**
  - –**Acute RNA pos but AB neg or pos**
  - –**60-80% persist: more in men, HIV pos, African ancestry, INFL4 gene intact**

Cox CID 2005

Hepatitis in a pilot

- **70 y/o pilot presents with 1 week of fever, diarrhea and sweats, then "collapses"**
- **Tooth extraction 1 month before, E. Shore of Maryland and extensive travel, chelation "treatment"**
- **T 38.1, 135/70, 85, 18, 97% on 2L; few small nodes, petechial rash on legs, neuro- WNL**

Pilot Case History, con't

- **Hct 33%, WBC 1.4 K (81% P 10% L), Plt 15,000**
- **Creat 2.8**
- **AST 495, ALT 159, Alk Phos 47, alb 2.6, TBR 0.8**
- **CPK 8477**
- **CXR: infiltrate LLL**

Hepatitis in a pilot

What agent caused this illness?

A. **Leptospira icterohaemorrhagiae**
B. **Hepatitis A**
C. **EBV**
D. **Ehrlichia chaffeensis**
E. **Hepatitis G (GB virus C)**

Hepatitis with bacterial infections

1. **Think Rickettsia/Ehrlichia with exposure, low PMN, and especially low platelets**

30 – Acute Hepatitis

Speaker: David Thomas, MD

Hepatitis with bacterial infections

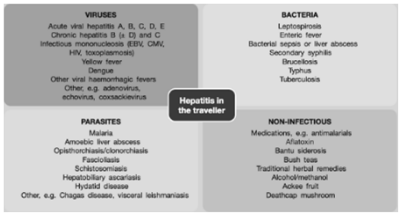
2. Coxiella burnetti and spirochetes (syphilis and lepto) also in ddx with liver, lung, renal, skin, CNS disease but tend to be cholestatic vs Rickettsia/Ehrlichia

Hepatitis with bacterial infections

3. Hepatitis F or G are WRONG answers

Hepatitis with travel to developing country

There is a broad differential



Jones Medicine 2017

Hepatitis with travel

Especially remember dengue (below), Chickungunya, or Zika

Ref.	Patients	Raised AST	Raised ALT	AST > ALT	Hyper-bilirubinemia	> 10 fold rise (AST, ALT)
Kuo et al[37]	270	93.30%	82.20%	+	7.20%	11.1%, 7.4%
Souza et al[39]	1585	63.40%	45%	+	-	3.4%, 1.8%
Itha et al[41]	45	96%	96%	Equal	30%	-
Wong et al[40]	127	90.60%	71.70%	+ in 75.6%	13.4%	10.2%, 9.5%
Parkash et al[33]	699	95%	86%	+	-	15%
Trung et al[36]	644	97%	97%	+	1.7%	-
Lee et al[14]	690	86%	46%	-	-	1%
Karoli et al[34]	138	92%		+	48%	-
Saha et al[35]	1226				16.9%	

Samanta World J Cases 2015

Hepatitis in Pregnancy

- **25yo G1P1 34 wks gestation with 1wk fever, chills, abd pain. 1 wk earlier cephalexin for GpB Strep.**
- **T 102; other vitals and exam as expected**
- **Plt 143K; Hb 8.6; WBC 6.4K 20% bands; glucose, creat and INR WNL; ALT 279; AST 643; TB 0.8.**
- **Hosp day 4:PLT 83K; PT 16; PTT 44; AST 2,240; ALT 980; BR nl; Fibrinogen NL;**

Allen OB GYN 2005

Hepatitis in pregnancy

What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. Atypical DRESS from cefelexin
D. HSV infection
E. HEV

30 – Acute Hepatitis

Speaker: David Thomas, MD

Hepatitis in pregnancy

1. Rule out HSV

~50% have muco-cutaneous lesions

High mortality without acyclovir

Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

ACOG 2016

Hepatitis in pregnancy

2. HELLP

- **HTN and can occur post partum**
- **Fibrinogen high vs. sepsis and AFLP**

3. AFLP – severe and low glucose, inc INR, low fibrinogen (Swansea criteria)

Fulminant hepatitis

- **65 year old man with hx of jaundice. 2 weeks before finished amoxacillin/clavulanate acid for sinusitis. Hx of HTN on HCTZ and rosuvastatin. ETOH: 2 drinks per day.**
- **TB24; ALT 162 U/L; AST 97 U/L ALK P 235 U/L. IgM anti-HAV neg; IgM anti-HBc neg; HCV RNA neg. RUQ US neg.**

Fulminant Hepatitis

Which of the following is the most likely cause of hepatitis:

A. toxicity from amox/clav
B. alcohol
C. porphyria flare
D. leptospirosis
E. statin

Drug related liver toxicity

Amoxicillin/clavulanate is most common

- **Cholestatic or mixed**
- **Often AFTER stopping**
- **1/2500 Rx**
- **DRB1*1501**
- **clavulanate>amoxicillin**

Rank	Agent	Year of FDA Approval	No. (%)†	Major Phenotypes
1	Amoxicillin-clavulanate	1984	91 (10.1)	Cholestatic or mixed hepatitis
2	Isoniazid	1952	48 (5.3)	Acute hepatocellular hepatitis
3	Nitrofurantoin	1953	42 (4.7)	Acute or chronic hepatocellular hepatitis
4	TMP-SMZ	1973	31 (3.4)	Mixed hepatitis
5	Minocycline	1971	28 (3.1)	Acute or chronic hepatocellular hepatitis
6	Cefazolin	1973	20 (2.2)	Cholestatic hepatitis
7	Azithromycin	1991	18 (2.0)	Hepatocellular, mixed, or cholestatic hepatitis
8	Ciprofloxacin	1987	16 (1.8)	Hepatocellular, mixed, or cholestatic hepatitis
9	Levofloxacin	1996	13 (1.4)	Hepatocellular, mixed, or cholestatic hepatitis
10	Diclofenac	1988	12 (1.3)	Acute or chronic hepatocellular hepatitis
11	Phenytoin	1946	12 (1.3)	Hepatocellular or mixed hepatitis
12	Methyldopa	1962	11 (1.2)	Hepatocellular or mixed hepatitis
13	Azathioprine	1968	10 (1.1)	Cholestatic hepatitis

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019

Acute Hepatitis Summary

- **Acute A: vaccine effective**
- **HEV: chronic in transplant and/or boar**
- **HIV: acute HCV in MSM**
- **Ehrlichial or rickettsial**
- **Find the lepto case (jaundice>hepatitis)**

30 – Acute Hepatitis

Speaker: David Thomas, MD

Thanks and good luck on the test!

Questions:

Dave Thomas

–dthomas@jhmi.edu

BREAK

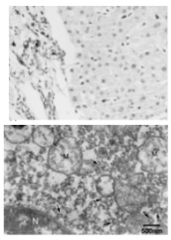
SLIDES BEYOND THIS ARE FOR THE PRESENTER'S RECORDS; NOT TO BE DISTRIBUTED OR SHOWN

Hepatitis in 2020: SARS-CoV-2

Table 2. **Laboratory and radiographic findings of patients with COVID-**

	All patients (N = 788)
Leukocytes, $\times 10^9$/L	4.8 (3.8-6.0)
Neutrophils, $\times 10^9$/L	3.0 (2.2-4.0)
Lymphocytes $\times 10^9$/L	1.2 (0.9-1.6)
$\geq 0.8 \times 10^9$/L	654 (83.0)
$<0.8 \times 10^9$/L	134 (17.0)
Platelets, $\times 10^9$/L	181 (147-221)
$\geq 100 \times 10^9$/L	761 (96.6)
$<100 \times 10^9$/L	27 (3.4)
Hemoglobin, g/L	138.0 (127.0-151.0)
International normalized ratio	1.02 (0.97-1.09)
Albumin, g/L	41.4 (38.3-43.8)
Alanine aminotransferase, U/L	21.1 (15.0-33.0)
Aspartate aminotransferase, U/L	25.0 (19.6-33.0)

Hao Am J Gastro 2020



Wang J Hepatol 2020

Case 6. Hepatitis in Pregnancy

- **24yo 33 wks gestation with nausea and vomiting and RUQ pain. Taking acetaminophen 1gm q6; has dog and bird; recent visit to mom in NC.**
- **T 37.2; BP 158/110;2/6 SEM; RUQ tender; no rash.**
- **Plt 103K; Hct 26; WBC 6.6 10%L; PMN 82%; G 85; creat 0.6; ALT 225; AST 559; TB 1.4; CRP 15.8; PT WNL; fibrinogen NL.**

Case 4: Tired and jaundiced

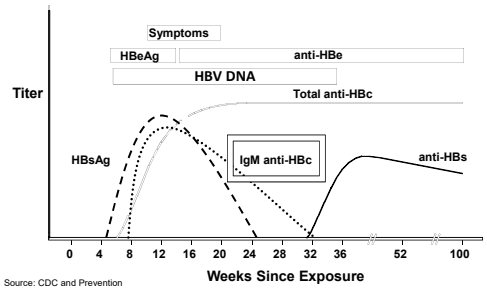
- **27 year old male presents with fatigue and dark urine. Hx recent sexual exposures with other men.**
- **No fever, vitals normal. Mild icteric. ALT 1945 IU/ml; AST 1239 IU/ml; TB 4.2 mg/dl; WBC 3.2k nl diff.**
- **Total HAV pos; HAV IgM neg; HCV RNA neg; IgM anti-HBc pos; HBsAg pos; RPR neg; HIV 4th gen neg**
- **Ptr was tested and is HBsAg and anti-HBs neg**

Question #4

Which is easiest to justify medically?

A. **Repeat HBsAg and anti-HBs testing for partner**
B. **HBIG and HBV vaccine for partner**
C. **HBV vaccine for partner**
D. **Entecavir 0.5 mg/d for patient**
E. **TAF for partner**

Diagnose acute HBV infection with IgM anti-HBc



2. No treatment indicated for acute HBV (unless fulminant)

3. Prevention by vaccine +/ HBIG

- HBsAg and anti-HBs screening of partners
- Tools: HBIG and/or HBV vaccine (USA)
  - Engerix, Recombivax, Heplisav-B, Pediarix, Twinrix
- Post-exposure:
  - Vaccinated and anti-HBs >10 ever, done*
  - No hx vaccine and/or anti-HBs >10, HBIG and vaccinate

*may be exception for patients with immunosuppression like HIV or dialysis

Schillie MMWR 2018

3. Prevention by vaccine +/ HBIG con't

- Pre-exposure:
  - no vaccine hx – vaccinate
  - Vaccine hx no testing – test for anti-HBs, boost or revaccinate if neg, retest anti-HBs

MMWR 2018

Acute hepatitis in HIV

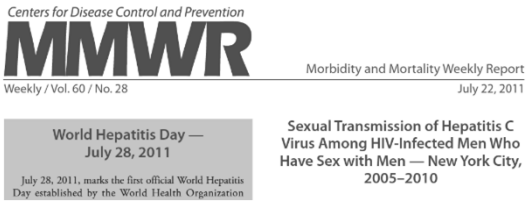
46 y/o HIV pos male, CD4+ lymphocyte 235/ml^3, HIV RNA undetect; HBsAg pos; no symptoms on TDF/FTC/RAL. Liver enzymes increased from ALT of 46 to 1041 IU/L. TB was 2.3. He has a long history of various ART regimens. He is sexually active with other men.

Acute hepatitis in HIV

Which of the following is the most likely cause of hepatitis:

A. toxicity from the RAL
B. acute HCV infection
C. IRIS
D. resistant HBV
E. HDV

Recognize acute HCV in HIV POS MSM


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 28
July 22, 2011

World Hepatitis Day — July 28, 2011

July 28, 2011, marks the first official World Hepatitis Day established by the World Health Organization

Sexual Transmission of Hepatitis C Virus Among HIV-Infected Men Who Have Sex with Men — New York City, 2005–2010

31

Viral and Bacterial Meningitis

Dr. Allan Tunkel

31 – Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Viral and Bacterial Meningitis

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

6/27/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE #1

2022 PREVIEW QUESTION

- 38-year-old woman presents with a 2-day history of fever, headache and stiff neck; similar episodes have occurred every 3-4 months over several years, with spontaneous abatement after 4-5 days
- She is sexually active only with her husband of 8 years, and has 2 children at home (ages 2 and 5 years)
- On exam, T 99.8ºF and other vital signs are normal; she has evidence of meningismus, but is alert and oriented and with no focal findings
- Laboratory studies are normal
- CSF analysis reveals a WBC of 70/mm^3 (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

QUESTION #1

2022 PREVIEW QUESTION

Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Human immunodeficiency virus
D. Herpes simplex virus type 2
E. Human herpesvirus 6

VIRAL MENINGITIS
Major Etiologies

- Enteroviruses
- Mumps virus
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Others
  - Arboviruses
  - Human immunodeficiency virus
  - Adenovirus
  - Parainfluenza virus types 2 and 3

Cerebrospinal Fluid (CSF) Findings in Viral Meningitis

CSF Parameter	Viral
Opening pressure	≤ 250 mm H_2O
WBC count	50-1000/mm^3
WBC differential	Lymphocytes
Glucose	>45 mg/dL
CSF: serum glucose	>0.6
Protein	<200 mg/dL
Gram stain	Negative

Enteroviruses

- Leading cause of "aseptic" meningitis syndrome
- Accounts for 85-95% of cases with identified etiology
- 30,000-75,000 cases annually in US (low estimate)
- Summer/fall seasonality; outbreaks reported
- Fecal-oral spread
- ~100 serotypes; 14 account for 80% of isolates
- CEMA (chronic enteroviral meningoencephalitis in agammaglobulinemia)
- Rituximab

Enteroviruses

- Clinical clues
  - Time of year
  - Outbreak in community
  - Other recognizable enteroviral syndromes
- Specific etiologies
  - Scattered maculopapular rash: echovirus 9
  - Herpangina: coxsackievirus A
  - Pericarditis/pleuritis: coxsackievirus B
  - Rhombencephalitis: enterovirus 71

Enteroviruses

- Symptoms and signs
  - Fever, headache, nuchal rigidity (>50%), photophobia
- Diagnosis
  - Neutrophils may predominate in CSF early (up to 48 hrs)
  - CSF virus isolation (sensitivity 65-75%)
  - Virus isolation from throat or rectum
  - PCR (sensitivity 86-100%; specificity 92-100%)
- Therapy
  - Supportive

Mumps Virus

- Common in unimmunized populations
- Occurs in 10-30% of mumps patients overall
- Peak in children 5-9 years of age; males>females
- Can occur in patients without parotitis; 40-50% have no evidence of salivary gland enlargement
- Symptoms and signs usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
  - Serology
  - CSF RT-PCR
  - CSF culture (sensitivity 30-50%)

Herpes Simplex Virus

- Self-limited syndrome
- Most commonly with primary HSV-2 genital infection
  - 36% of women
  - 13% of men
- Less likely with recurrence of genital herpes
- Recurrent benign lymphocytic meningitis (Mollaret)
  - Most caused by HSV-2
  - Few or at least 10 episodes lasting 2-5 days followed by spontaneous recovery
  - Fever, headache, photophobia, meningismus

Herpes Simplex Virus

- Diagnosis
  - Lymphocytic pleocytosis (<500 cells/mm^3); normal glucose, elevated protein
  - CSF PCR
- Therapy
  - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis
  - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

Lymphocytic Choriomeningitis Virus

13

- Now rarely reported as an etiologic agent
- Transmitted to humans by contact with rodents (hamsters, rats, mice) or their excreta
- As estimated 5% of house mice in the US are infected; infection more common in winter when mice are indoors
- Risk groups
  - Laboratory workers
  - Pet owners
  - Persons living in impoverished or unhygienic places
  - Rodent breeding factory
- No evidence of human-to-human transmission

CASE #2

14

- 60-year-old man with chronic kidney disease immigrated from Brazil to the US and underwent a cadaveric renal transplant
- Prior to transplant, he had episodes of recurrent epigastric pain. At the time, his WBC was 6,500/mm^3 with 15% eosinophils
- After transplant, he received immunosuppressive therapy

CASE #2

15

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39°C
- Lumbar puncture had WBC 2500/mm^3 (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL
- Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
- Cultures of blood and CSF grew *Escherichia coli*

Question #2

16

Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?

A. MRI of the head and sinuses
B. Right upper quadrant ultrasound
C. Serial stool examinations
D. Cisternography
E. Colonoscopy

EPIDEMIOLOGIC FEATURES OF PNEUMOCOCCAL MENINGITIS

17

- Most common etiologic agent in US (58% of cases)
- Mortality of 18-26%
- Associated with other suppurative foci of infection
  - Pneumonia (25%)
  - Otitis media or mastoiditis (30%)
  - Sinusitis (10-15%)
  - Endocarditis (<5%)
  - Head trauma with CSF leak (10%)

EPIDEMIOLOGIC FEATURES OF MENINGOCOCCAL MENINGITIS

18

- Children and young adults; mortality 3-13%
- Serogroups A, B, C, W, and Y
- Serogroup B disease in recent outbreaks
- Predisposition in those with congenital deficiencies in terminal complement components (C5-C8, and perhaps C9) and properdin deficiencies
- Increased risk: MSM, HIV infection, use of complement inhibitors that block C5 (eculizumab, ravulizumab), microbiologists exposed to isolates, travel to epidemic or hyperendemic areas, outbreak-related, college students

31 – Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

EPIDEMIOLOGIC FEATURES OF GROUP B STREPTOCOCCAL MENINGITIS

19

- Important etiologic agent in neonates; mortality 7-27%
- Early-onset septicemia associated with prematurity, premature rupture of membranes, low birth weight
- Late onset meningitis (> 7 days after birth)
- Disease in adults associated with the following:

Diabetes mellitus
Parturient women
Cardiac, hepatic, renal disease
Malignancy
Collagen-vascular disorders
Alcoholism
HIV infection
Corticosteroid use

EPIDEMIOLOGIC FEATURES OF *LISTERIA* MENINGITIS

20

- Rare etiology in US (2-8%); mortality 15-29%
- Outbreaks associated with consumption of contaminated cole slaw, raw vegetables, milk, cheese, processed meats, cantaloupe, diced celery, ice cream, hog head cheese
- Common in neonates
- Low in young, previously healthy persons (4-10%)
- Disease in adults associated with:

Elderly
Alcoholism
Malignancy
Immune suppression
Diabetes mellitus
Hepatic and renal disease
Iron overload
Collagen-vascular disorders
HIV infection
Biologic therapies

EPIDEMIOLOGIC FEATURES OF AEROBIC GRAM-NEGATIVE BACILLARY MENINGITIS

21

- *Klebsiella* species, *Escherichia coli*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Salmonella* species
- Isolated from CSF of patients following head trauma or neurosurgical procedures, and from patients with CSF shunts or drains
- Cause meningitis in neonates, the elderly, immunocompromised patients, and in patients with gram-negative septicemia
- Associated with disseminated strongyloidiasis in the hyperinfection syndrome

EPIDEMIOLOGIC FEATURES OF *HAEMOPHILUS INFLUENZAE* MENINGITIS

22

- Causes 7% of cases in US; mortality 3-7%
- Capsular type b strains were previously in >90% of serious infections; children <6 years of age (peak 6-12 months)
- Concurrent pharyngitis or otitis media in >50% of cases
- Disease in persons >6 years of age associated with:

Sinusitis or otitis media
Pneumonia
Sickle cell disease
Splenectomy
Diabetes mellitus
Immune deficiency
Head trauma with CSF leak
Alcoholism

OTHER BACTERIAL ETIOLOGIES OF MENINGITIS

23

Bacterial Etiology	Risk Factors
Staphylococcus aureus	Neurosurgery, trauma, diabetes mellitus, alcoholism, hemodialysis, injection drug use, malignancy
Staphylococcus epidermidis	CSF shunts and drains
Diphtheroids (e.g., *Cutibacterium acnes*)	CSF shunts and drains
Anaerobes	Contiguous foci in head and neck
Streptococcus salivarius	Spinal anesthesia, myelogram
Streptococcus suis	Vietnam, eating undercooked pig blood or pig intestine, pig exposure

INCIDENCE OF BACTERIAL MENINGITIS (UNITED STATES)

24

Organism	Incidence (cases per 100,000)		
	1986	1995	2006-2007
H. influenzae	2.9	0.2	0.08
S. pneumoniae	1.1	1.1	0.81
N. meningitidis	0.9	0.6	0.19
Group B streptococcus	0.4	0.3	0.25
L. monocytogenes	0.2	0.2	0.05

CEREBROSPINAL FLUID FINDINGS IN BACTERIAL VERSUS VIRAL MENINGITIS

25

CSF Parameter	Bacterial	Viral
Opening pressure	200-500 mm H_2O	≤ 250 mm H_2O
WBC count	1000-5000/mm^3	50-1000/mm^3
WBC differential	Neutrophils	Lymphocytes
Glucose	<40 mg/dL	>45 mg/dL
CSF: serum glucose	≤ 0.4	>0.6
Protein	100-500 mg/dL	<200 mg/dL
Gram stain	(+) in 60-90%	Negative

CASE #3

IDBR 2022 PREVIEW QUESTION

26

- A 35-year-old woman presents to the hospital with a 2-day history of fever, chills, headache, and mild confusion. She had head trauma several weeks earlier, associated with clear fluid draining out of her nose
- T 40.5ºC, P 140, RR 32, BP 90/60 mmHg
- Obtunded, stiff neck
- WBC 30,000/mm^3 (40% bands), platelets 20,000/mm^3
- Lumbar puncture revealed an opening pressure of 400 mm H_2O, WBC 2500/mm^3 (99% segs), glucose 20 mg/dL, and protein 400 mg/dL

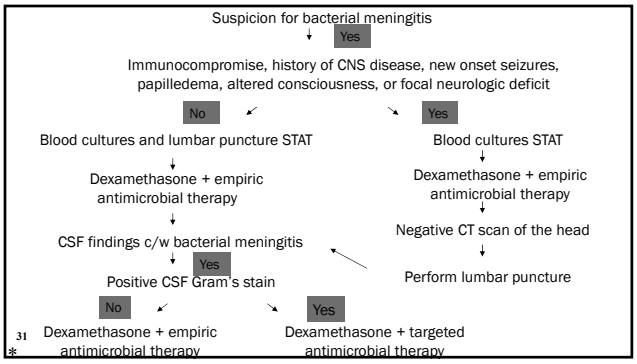
Question #3

IDBR 2022 PREVIEW QUESTION

27

Which of the following empiric antimicrobial regimens should be initiated?

A. Ampicillin
B. Ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone
E. Vancomycin + ciprofloxacin



31 *

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

29

Age	Antimicrobial Therapy
<1 month	Ampicillin + gentamicin + either cefotaxime (if available) or cefepime
1-23 months	Vancomycin + a third-generation cephalosporin[a]
2-50 years	Vancomycin + a third-generation cephalosporin[a,b,c]
Older than 50 years	Vancomycin + ampicillin + a third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime
[b]some experts would add rifampin if dexamethasone is also given
[c]add ampicillin if Listeria is suspected

EMPIRIC ANTIMICROBIAL THERAPY OF PURULENT MENINGITIS

30

Predisposing Condition	Antimicrobial Therapy
Immunocompromise	Vancomycin + ampicillin + either meropenem or cefepime
Basilar skull fracture	Vancomycin + a third generation cephalosporin[a]
Head trauma or after neurosurgery	Vancomycin + either ceftazidime or cefepime or meropenem
Cerebrospinal fluid shunt or drain	Vancomycin + either ceftazidime or cefepime or meropenem

[a]ceftriaxone or cefotaxime

31 – Viral and Bacterial Meningitis

Speaker: Allan Tunkel, MD

TARGETED ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

31

Microorganism	Antimicrobial Therapy
S. pneumoniae	Vancomycin + a third-generation cephalosporin[a,b]
N. meningitidis	Third-generation cephalosporin[a]
H. influenzae	Third-generation cephalosporin[a]
L. monocytogenes	Ampicillin or penicillin G[c]

[a]ceftriaxone or cefotaxime
[b]addition of rifampin may be considered, especially if dexamethasone given
[c]addition of an aminoglycoside may be considered

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

32

Organism	Antimicrobial Therapy
Streptococcus pneumoniae	
PCN MIC ≤0.06 μg/mL	Penicillin G or ampicillin
PCN MIC ≥0.12 μg/mL	
CTX[a] MIC <1.0 μg/mL	Third-generation cephalosporin[a]
CTX[a] MIC ≥1.0 μg/mL	Vancomycin + a third-generation cephalosporin[a,b]

[a]ceftriaxone or cefotaxime
[b]consider addition of rifampin if ceftriaxone MIC ≥4 μg/mL

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

33

Organism	Antimicrobial Therapy
Neisseria meningitidis	
PCN MIC <0.1 μg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 μg/mL	Third-generation cephalosporin[a]
Haemophilus influenzae	
β-lactamase-negative	Ampicillin
β-lactamase-positive	Third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime

ANTIMICROBIAL THERAPY IN BACTERIAL MENINGITIS

34

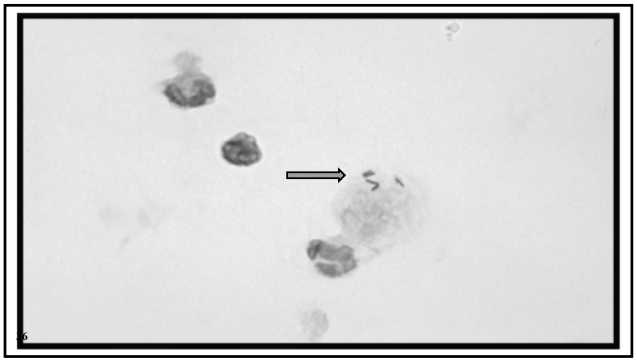
Organism	Antimicrobial Therapy
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Acinetobacter baumannii	Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a]
Streptococcus agalactiae	Ampicillin or penicillin G
Listeria monocytogenes	Ampicillin or penicillin G[b]
Staphylococcus aureus	
MSSA	Nafcillin or oxacillin
MRSA	Vancomycin

[a]might also need to be administered by intraventricular or intrathecal routes
[b]addition of an aminoglycoside should be considered

CASE #4

35

- 60-year-old male with chronic lymphocytic leukemia presented with fever, headache, ataxia, and altered mental status. Recently traveled to an outdoor family picnic in rural Virginia. He is allergic to penicillin (anaphylaxis)
- T 102°F, P 120, RR 24, BP 100/60 mmHg
- He was obtunded and had nuchal rigidity
- WBC was 25,000/mm^3 (30% bands)
- LP revealed a WBC 1500/mm^3 (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL



36

Question #4

37

Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

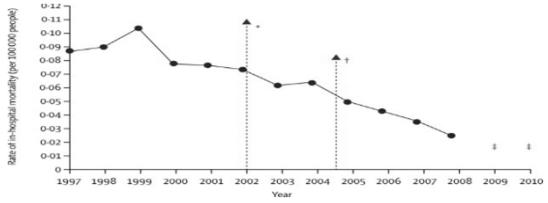
ADJUNCTIVE DEXAMETHASONE IN BACTERIAL MENINGITIS

38

- Attenuates subarachnoid space inflammatory response resulting from antimicrobial-induced lysis
- Recommended for infants and children with *Haemophilus influenzae* type b meningitis and considered for pneumococcal meningitis in childhood, given before or with parenteral antimicrobial therapy
- Recommended in adults with pneumococcal meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose

IN-HOSPITAL MORTALITY FOR PNEUMOCOCCAL MENINGITIS

39



Castelblanco et al. Lancet ID 2014;14:813

40 QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

32

Chronic Hepatitis

Dr. David Thomas

32– Chronic Hepatitis

Speaker: David Thomas, MD

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Chronic Hepatitis

David L. Thomas, MD
Stanhope Bayne Jones Professor of Medicine
Johns Hopkins University
Chief of Infectious Diseases
Johns Hopkins School of Medicine

7/10/2022

INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Disclosures of Financial Relationships with Relevant Commercial Interests

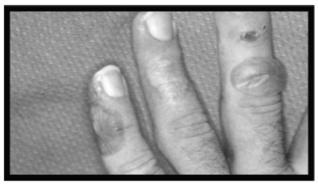
- Data and Safety Monitoring Board: Merck
- Advisory Board: Merck and Excision Bio

Chronic Hepatitis and Liver Disease

- HCV
- HBV (and delta)
- Other forms
- HIV coinfection

Case: Hepatitis C and a rash

A 44 year old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge. He has a chronic rash on arms that is worse and elevated ALT and AST.



OConnor Mayo Clin Proc 1998

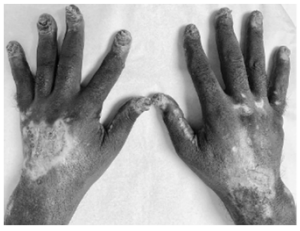
Question: HCV with a rash

The most likely dx is:

A. Cirrhosis due to HCV and alcohol
B. Necrolytic acral erythema
C. Porphyria cutanea tarda
D. Essential mixed cryoglobulinemia
E. Yersinia infection

Porphyria Cutanea Tarda Associated with Hepatitis C

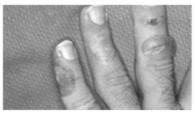
Tejesh S. Patel, M.D., and Evgeniya Teterina Mohammed, M.D.



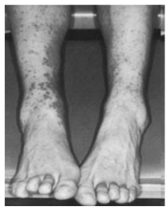
June 10, 2021
N Engl J Med 2021; 384:e86

Compare

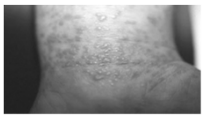
Porphyria cutanea tarda



Cryoglobulin vasculitis



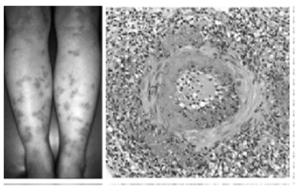
Lichen planus



blogspot.com; OConnor Mayo Clin Proc 1998

Case: HBV and rash

46 year old woman HBsAg pos, anti-HCV neg



Chen Rheum 2014

Question: HBV with a rash

The most likely dx is:

A. **Necrolytic acral erythema**
B. **Porphyria cutanea tarda**
C. **Essential mixed cryoglobulinemia**
D. **Polyarteritis nodosa**
E. **Secondary syphilis vasculitis**

Question: Who needs an HCV antibody test?

A. **33 year old woman with normal ALT and negative test during pregnancy at 28**
B. **55 year old man with new exposure after HCV treatment**
C. **24 year old pregnant woman with no risk factors**
D. **Former PWID who was HCV negative 1 yr ago**
E. **HIV positive MSM with negative HCV antibody test 5 years ago and no risk factors**

IDSA/AASLD guidelines

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

USPSTF 2020

RECOMMENDATION The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

JAMA. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

PREVIEW QUESTION

Case: 54 y/o with HCV antibodies and RNA

54 year old man was anti-HCV pos after elevated ALT noted by primary. Brief IDU when 20-21; moderate ETOH; otherwise well.

HCV RNA 4 million IU/L; Genotype 1a; ALT 42 IU/ml; AST 65 IU/ml; TB 1.6 mg/dl; Alb 3.9 mg/dl; Hb – 13.4 mg/dl; creatinine 1.2 mg/dl; HBsAg pos; anti-HBc pos. HIV neg

2022 PREVIEW QUESTION

Question: 54 y/o with HCV antibodies and RNA

Which of the following is the next appropriate step:

A. **Treat with oral regimen for 8-12 weeks**
B. **Check HCV 1a resistance test**
C. **Elastography**
D. **Confirm HCV antibody test**

HCV NS5 RAS testing is uncommonly recommended

Treatment naive	*Treatment experienced*
• Genotype 1a and elbasvir/grazoprevir	• 1a and ledipasvir/sofosbuvir 'considered'
• Genotype 3 AND cirrhosis for sofosbuvir/velpatasvir	• Genotype 3 and sofosbuvir/velpatasvir

NB: no PI resistance testing
Clinically sig is >100-fold in vitro

Wyles, HCVguidelines.org

Staging is needed for chronic HCV

Accepted staging methods	Not for routine staging
1. Liver biopsy	1. Viral load
2. Blood markers	2. HCV genotype
3. Elastography	3. Ultrasound
4. Combinations of 1-3	4. CT scan or MRI

Hcvguidelines.org

$$\text{FIB 4} = \frac{\text{Age (yrs) x AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x ALT (U/L)}^{1/2}}$$

847 liver biopsies with chronic HCV

	Liver Biopsy (METAVIR)		
FIB4 Index	F0-F1-F2	F3-F4	Total
<1.45	94.7% (n = 521)	5.3% (n = 29)	550
1.45-3.25	73.0% (n = 168)	27.0% (n = 62)	230
>3.25	17.9% (n = 12)	82.1% (n = 55)	67
Total	82.8% (n = 701)	17.2% (n = 146)	847

Sterling Hepatology 2006; Vallet-Pichard Hepatology 2007

Of imperfect tests elastography is most sensitive for detection of cirrhosis

Test	% Sens	% Spec	AUROC
Fibrotest[1] >.56	85	74	.86
Fibrotest > .73	56	81	-
FIB4[2], >1.45	87	61	.87
APRI[3], >1.0	51	91	0.73
Elastography 12.5 kPa	89	91	0.95

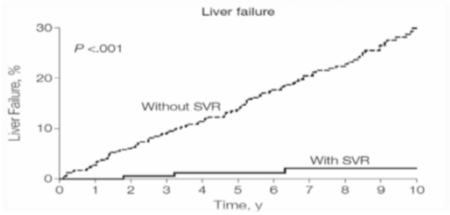
Singh Gastro 2017; Chou Ann Intern Med 2013; Castera Gastro 2012

Case con't: 54 year old with HCV

Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis. Ultrasound and UGI are ok and you recommend treatment. He wants to know why. Which can you NOT say is true of successful treatment?

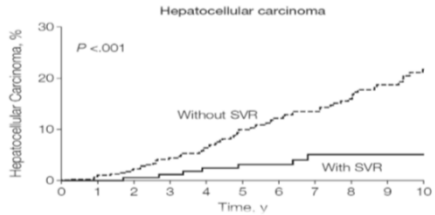
A. **reduces risk of reinfection**
B. **reduces risk of death**
C. **reduces risk of HCC**
D. **reduces risk of liver failure**

SVR reduces clinical outcomes



Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SVR reduces clinical outcomes



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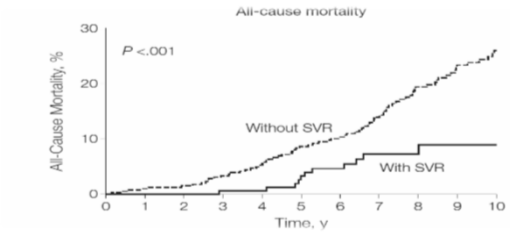
SVR reduces clinical outcomes



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AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

54 y/o with HCV antibodies, RNA, and cirrhosis

Treatment is given with glecaprevir and pibrentasvir

Treatment week 8: HCV RNA undet; ALT 1279 IU/L; AST 987 IU/L; TB 3.2 mg/dl.

Which test is likely to be most helpful?

A. Glecaprevir level
B. HCV resistance test
C. HCV IRIS T cell marker
D. HBV DNA
E. Liver biopsy with EM

FDA U.S. Food and Drug Administration Protecting and Promoting Your Health — Drug Safety Communications

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

All are tested for HBV

- HBsAg pos: treat per HBV guidelines
- Anti-HBc pos: monitor

Bersoff-Macha Ann Intern Med 2017; Thio and Balagopal CID 2015

Which is NOT a pangenotypic regimen?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

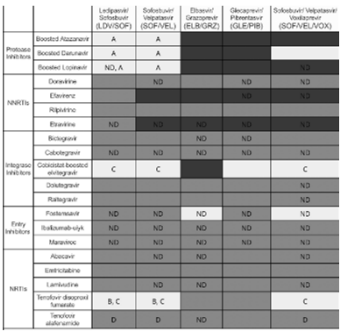
Which regimen is approved for ESRD?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir
D. All of the above

Which regimen is worst with darunavir?

A. Glecaprevir and pibrentasvir
B. Sofosbuvir and velpatasvir
C. Sofosbuvir and ledipasvir

HCV-HIV ART drug interactions



		Ledipasvir/ Sofosbuvir (LDV/SOF)	Sofosbuvir/ Velpatasvir (SOF/VEL)	Elbasvir/ Grazoprevir (EBR/GRZ)	Glecaprevir/ Pibrentasvir (GLE/PIB)	Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX)
Protease inhibitors	Boosted Atazanavir	A	A			
	Boosted Darunavir	A	A			
	Boosted Lopinavir	NO, A	A			ND
NNRTIs	Doravirine		ND		ND	ND
	Efavirenz				ND	ND
	Rilpivirine					
	Etravirine	ND	ND	ND	ND	ND
Integrase inhibitors	Bictegravir			ND	ND	
	Cabotegravir	ND	ND	ND	ND	ND
	Cobicistat-boosted elvitegravir	C	C			C
	Dolutegravir					ND
	Raltegravir					ND
Entry inhibitors	Fostemsavir	ND	ND	ND	ND	ND
	Ibalizumab-uiyk	ND	ND	ND	ND	ND
	Maraviroc	ND	ND	ND	ND	ND
NRTIs	Abacavir		ND	ND		ND
	Emtricitabine					
	Lamivudine		ND	ND		ND
	Tenofovir disoproxil fumarate	B, C	B, C			C
	Tenofovir alafenamide	D	D	ND		D

www.hcvguidelines.com

Slide 28 of 44

HCV treatment summary 2022

- Test, stage, and treat
- Two pangenotypic regimens: SOF/VEL and GP
- Watch for HBV relapse at week 8
- No change for HIV (avoid drug interactions), renal insufficiency, acute infection
- Compensated cirrhosis same for G/P and Sof-based except GT3 with resistance

Case of chronic hepatitis B

31 yr old Asian woman is referred to see you because she had a positive HBsAg test. She is otherwise feeling fine.

HBsAg pos, HBeAg neg, anti-HBe pos, ALT 78 IU/ml, AST 86 IU/ml, TB 0.8, albumin 4.2 g/dl, INR 1.

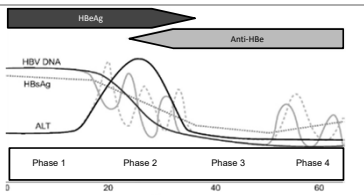
Which of the following tests is NOT recommended?

A. HIV test
B. HBV resistance
C. HBV genotype
D. Hepatitis Delta testing
E. Quantitative HBV DNA level

The essential evaluation of persons with CHB

- HBeAg, HIV, HBV DNA, delta, genotype
- Stage (liver enzymes and/or elastography or biopsy)
- Renal status
- US to r/o HCC
  - Asian: male 40; female 50
  - African: 25-30

Use testing to define disease phase[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Use testing to define disease phase

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Use disease phase to determine whom to treat

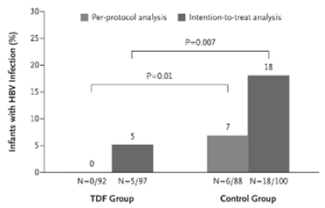
Chronic HBV infection	HBeAg positive		HBeAg negative	
	Phase 1	Phase 2	Phase 3	Phase 4
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated†

Treat with both high DNA and ALT

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persistently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

Test pregnant women for HBsAg and, if pos, for HBV DNA* and treat if > 200,000 IU/ml

Rec for all pregnant women to have quantitative HBV DNA TEST



*test in 3rd trimester

Terrault Hepatology 2015; Pan NEJM 2016

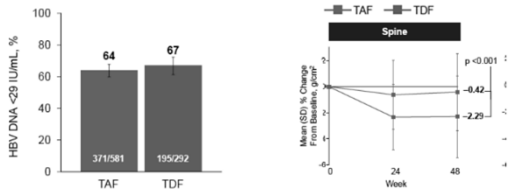
Four preferred treatments for chronic hepatitis B

HBeAg Positive	Peg-IFN*	Entecavir†	Tenofovir Disoproxil Fumarate†	Tenofovir Alafenamide‡
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	30-42 (<2,000-40,000 IU/mL) 8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	—	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	—
% HBsAg loss	2-7 11 (at 3 years posttreatment)	4-5	8	1
HBeAg Negative	**Peg-IFN**	**Entecavir**	**Tenofovir Disoproxil Fumarate†**	**Tenofovir Alafenamide‡**
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)§	43 (<4,000 IU/mL) 19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 IU/mL)	90 (<29 IU/mL)
% Normalization ALT¶	59	78-88	76	81
% HBsAg loss	4 6 (at 3 years posttreatment)	0-1	0	<1

TAF 25 mg with or without FTC

AASLD guidelines, Terrault Hepatology 2018

TAF is as effective and safer than tenofovir DF for chronic hepatitis B



Chan Lancet Gastro 2016

Treatment of HBV changes with renal insufficiency

- **GFR 30-60 mL/min/1.73 m²** : TAF 25 mg preferred
- **GFR <30-10:** TAF 25mg OR entecavir 0.5 mg q 3d
- **GFR <10 no dialysis:** entecavir 0.5 mg
- **Dialysis:** TDF 300mg/wk PD or entecavir 0.5mg/wk or TAF 25mg PD

It is hard to stop HBV treatment

- **If HBeAg conversion noted and no cirrhosis *consider* stopping after 6 months**
- **HBeAg neg when treatment started and all with cirrhosis stay on indefinitely**

HIV/HBV coinfected need treatment for both

- **<u>All</u> are treated and tested for both**
- **HBV-active ART**
- **Entecavir less effective if LAM exposure**
- **Watch switch from TAF- or TDF-containing regimen**

What if HBV levels stay detectable?

- **Continue monotherapy, ideally with TAF or TDF**
- **Rising levels (breakthrough)**
  - **Add second drug or switch esp if initial Rx with ETV**

2022 PREVIEW QUESTION

Hepatitis serology in the oncology suite

You are called about 62 year old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non Hodgkins lymphoma.

Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

2022 PREVIEW QUESTION

What do you recommend?

A. Hold rituximab
B. Hold prednisone
C. Entecavir 0.5 mg
D. HCV PCR
E. HBV DNA

HBV Reactivation with immunosuppression

Rituximab, high dose corticosteroids, and BMT/solid organ transplant high risk for HBV reactivation

- If HBsAg pos, prophylaxis *always* recommended
- If anti-HBc pos but HBsAg neg, prophylaxis still recommended with high risk exposures
- Use TAF or ETV

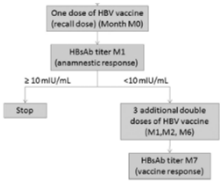
AASLD Terrault Hepatology 2018

Isolated anti-core antibodies usually reflect occult hepatitis B in high risk groups

- Primary responses to vaccination
- 29 anti-HBc and 40 negative for anti-HBc
  - anamnestic response in anti-HBc pos (24%) vs anti-HBc neg (10%)
  - 50% anti-HBc pos also tested positive for anti-HBe
  - Anti-HBs seroconversion in ~60% both groups

Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV vaccination recommended in persons with isolated anti-HBc



Gandhi JID 2005; Terrault Hepatology 2018; Piroth CID 2018

HBV Prevention is with vaccine and sometimes HBIG

Pre-exposure:
- vaccinate ALL < 60 yrs and get post vaccination titers (<2 months) if exposure likely
- Engerix; Recombivax; Heplisav (2 dose); PreHevbrio; Twinrix

Post Exposure:
- vaccinate if not already done or not known to respond
- add HBIG when infection likely
- infants of HBsAg pos mothers get immediate vaccination and HBIG

MMWR April 1, 2022 71 (13) 477-483; MMWR / January 12, 2018 / Vol. 67 / No. 1

32– Chronic Hepatitis

Speaker: David Thomas, MD

Chronic Hepatitis for the Boards Summary

- HCV-associated conditions: PCT or cryoglobulinemia
- HBV-associated: PAN
- HCV: staging or treatment outcome
- HBV: relapse post rituximab
- Guess b and good luck

Thanks and good luck on the test!

Questions:

Dave Thomas

–dthomas@jhmi.edu

BONUS CASE

A final case of chronic hepatitis in transplant recipient

51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid. Hunts wild boar in Texas

HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

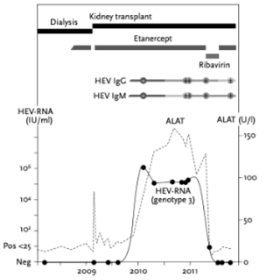
Barrague Medicine 2017

Which test is most likely abnormal

1. **HEV PCR**
2. **HCV IgM**
3. **Tacrolimus level**
4. **Adenovirus PCR**
5. **Delta RNA PCR**

Chronic HEV in transplant recipient

- **Europe (boar)**
- **Can cause cirrhosis**
- **Tacrolimus associated**
- **Ribavirin may be effective**



Barrague Medicine 2017

33

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Dr. Allan Tunkel

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema and Epidural Abscess

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

6/27/2022

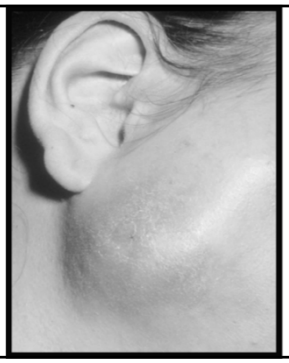
IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

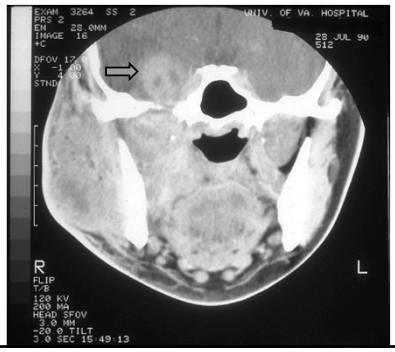
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

CASE #1

- 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks. She was unable to open her mouth. She denied fever or headache, and had no past hospitalizations or illnesses. The patient had not been to the dentist within 10 years.
- T 99.8°F, P 88, RR 14, BP 110/80
- Exam revealed swelling and erythema along her right mandible





Question #1 (Case #1)

Which of the following empiric antimicrobial regimens should be initiated?

A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

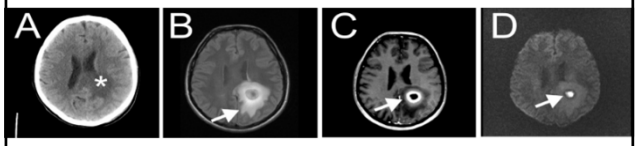
Speaker: Allan Tunkel, MD

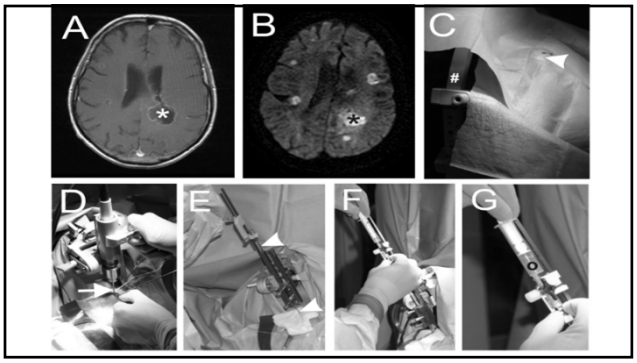
PREDISPOSING CONDITIONS FOR BRAIN ABSCESS

Condition	Relative Frequency (%)
Contiguous focus of infection (otitis media, mastoiditis, sinusitis, face or scalp infection, dental sepsis, osteomyelitis, penetrating head injury)	30-50
Hematogenous spread (lung abscess, empyema, congenital heart disease, bronchiectasis, infective endocarditis, compromised host, hereditary hemorrhagic telangiectasia)	~35
Cryptogenic	10-35

PRINCIPLES OF BRAIN ABSCESS MANAGEMENT

- MR imaging is the diagnostic procedure of choice; diffusion-weighted imaging increases diagnostic accuracy (sensitivity and specificity 96% for differentiation from cancers [PPV 98%; NPV 92%])
- Lumbar puncture is contraindicated
- Biopsy or aspiration (via stereotactic guidance) is needed for microbiologic diagnosis
- Begin empiric antimicrobial therapy based on underlying condition and pathogenesis of spread of infection to brain





EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Predisposing Condition	Antimicrobial Regimen
Otitis media or mastoiditis	Metronidazole + a third-generation cephalosporin[a]
Sinusitis	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Third-generation cephalosporin[a] + metronidazole
Penetrating trauma or post-neurosurgical	Vancomycin + a third or fourth generation cephalosporin
Lung abscess, empyema, bronchiectasis	Third-generation cephalosporin[a] + metronidazole + trimethoprim-sulfamethoxazole
Bacterial endocarditis	Vancomycin[b]

[a]ceftriaxone or cefotaxime
[b]additional agents may be used based on other likely microbial etiologies

EMPIRIC ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

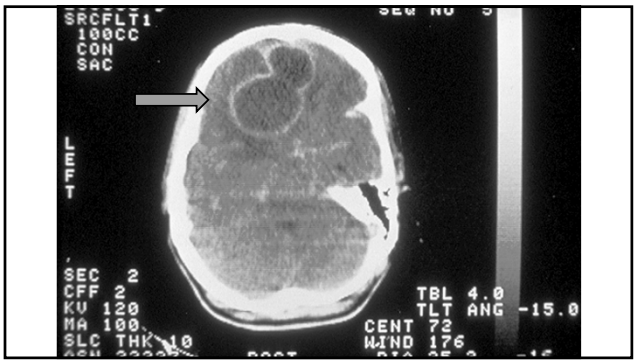
Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin
Transplant recipients	Add voriconazole, plus trimethoprim-sulfamethoxazole or sulfadiazine
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

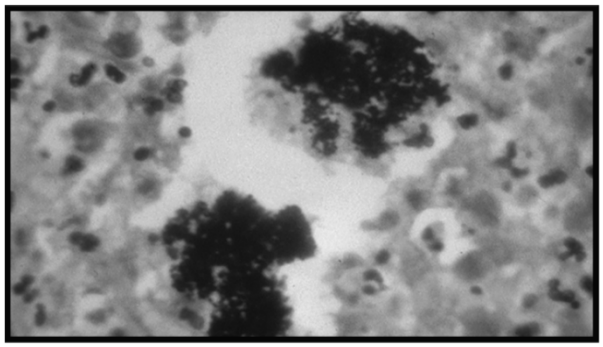
33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CASE #2

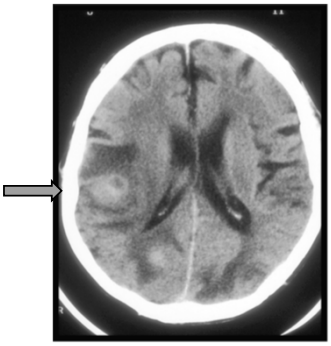
- 21-year-old member of a motorcycle gang thrown from his bike, and suffered a depressed skull fracture
- In the OR, a large subdural hematoma was evacuated
- Discharged in 5 days
- Returned by mother 5 days later because of bizarre behavior
- No headache, afebrile

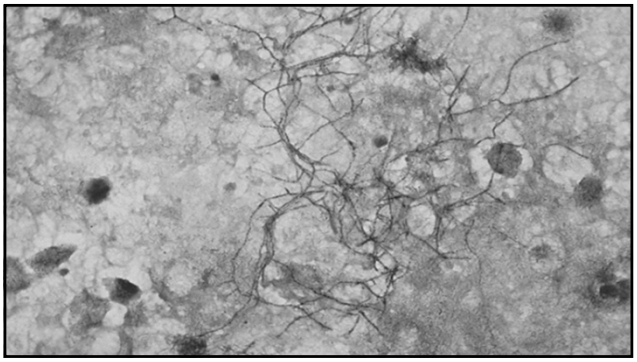




CASE #3

- 78-year-old male with multiple myeloma on chronic prednisone therapy; underwent aortic valve replacement with a bioprosthesis 5 years earlier; presented with new-onset seizures
- T 100.4º 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 + ampicillin + gentamicin
- Blood cultures negative





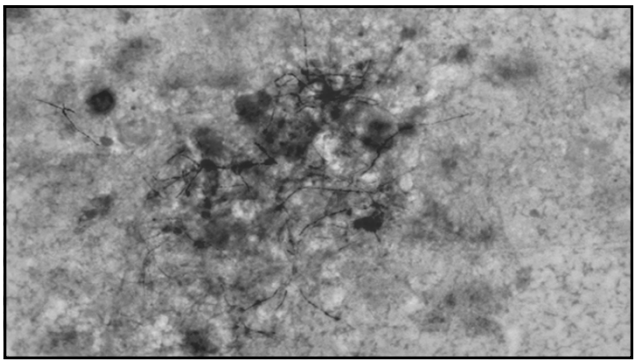
33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

Question #2 (Case #3)

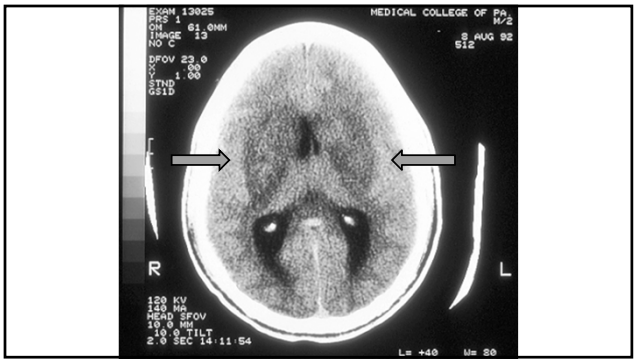
Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole
C. Daptomycin
D. Liposomal amphotericin B + 5-FC
E. Voriconazole



CASE #4

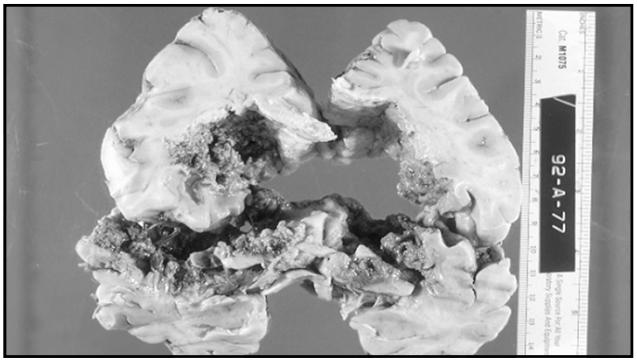
- 24-year-old injection drug user who, while injecting intravenous drugs with his girlfriend, fell out of the second story window of his apartment. When he did not return for 48 hours, she found him unresponsive on the ground and called fire rescue
- T 103°F, P 150, RR 32, BP 110/76 mmHg
- On exam, he was comatose without evidence of head trauma
- WBC 13,000/mm^3, profound metabolic acidosis



Question #3 (CASE #4)

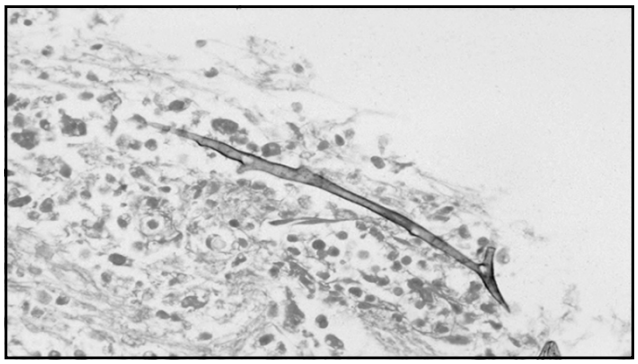
The most likely etiologic agent of the patient's CNS lesions is which of the following?

A. Staphylococcus aureus
B. Pseudomonas aeruginosa
C. Nocardia asteroides
D. Candida albicans
E. Rhizopus arrhizus



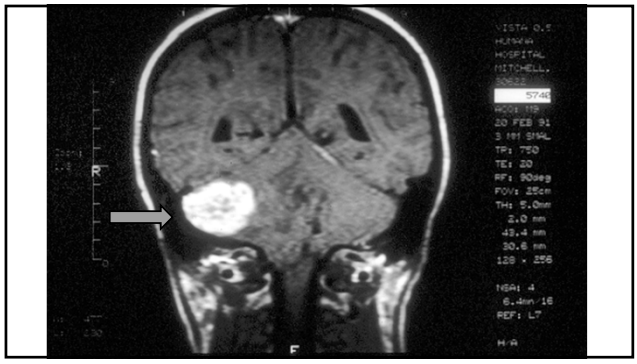
33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

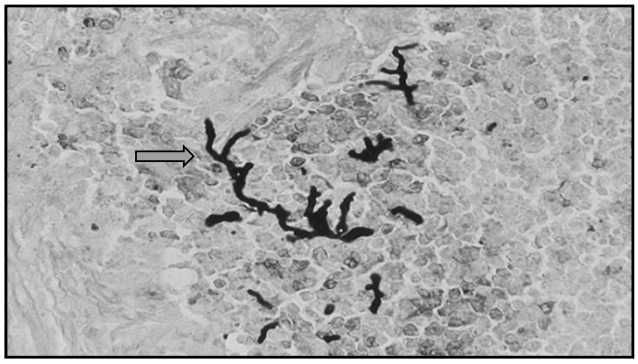
Speaker: Allan Tunkel, MD



CASE #5

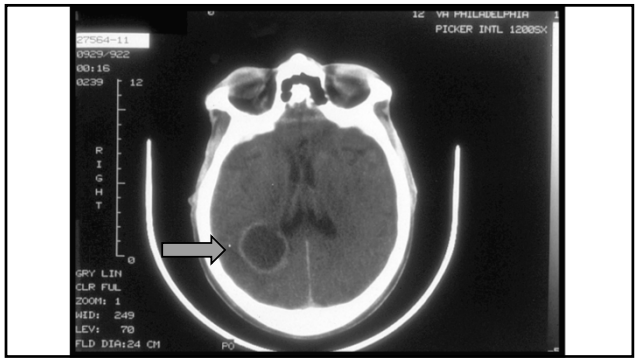
- 11-year-old boy with chronic granulomatous disease on chronic TMP-SMX therapy noted the onset of a mild headache which lasted 10 minutes.
- Two weeks later at a routine physician visit, the patient had no complaints and denied recurrence of the headache
- On examination, the patient had normal vital signs and a normal neurologic examination
- The physician ordered an MR imaging of the head





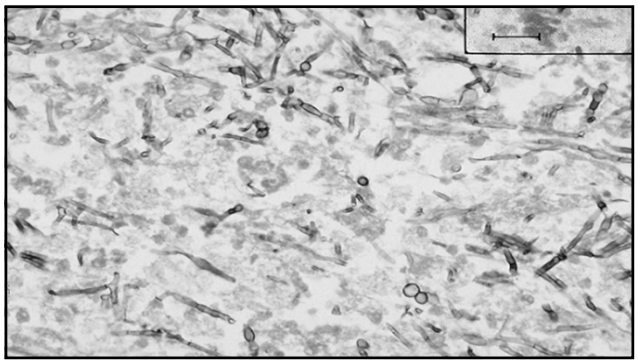
CASE #6

- 80-year-old male with CLL on chronic prednisone therapy presented to the VA Hospital with sepsis and ARDS. Course complicated by VDRF and multiple nosocomial infections, including candidemia for which he received 4 weeks of IV liposomal amphotericin B. After completing the course of therapy, he developed altered mental status
- T 101^0 F, P 100, RR 20, BP 120/76
- Neurologic exam left-sided hyperreflexia and Babinski



33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD



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
Enterobacteriaceae[a]	Third or fourth generation cephalosporin
Fusobacterium sp.[a]	Metronidazole
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus aureus	Nafcillin, oxacillin, or vancomycin
Strep. milleri; [a] other streptococci[a]	Penicillin G

[a]depending on pathogenesis of infection, may be isolated as part of a mixed infection

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Nocardia asteroides	Trimethoprim-sulfamethoxazole or sulfadiazine; combination therapy for immunocompromised patients and those failing standard therapy
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide ± ethambutol

ANTIMICROBIAL THERAPY OF BRAIN ABSCESS

Organism	Antimicrobial Therapy
Aspergillus sp.	Voriconazole
Candida sp.	Lipid formulation of amphotericin B[a]
Mucorales	Lipid formulation of amphotericin B
Scedosporium spp.	Voriconazole

[a]Addition of 5-flucytosine should be considered

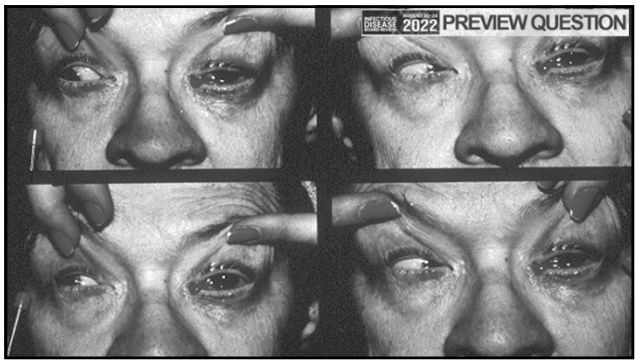
CASE #7

2022 PREVIEW QUESTION

- 79-year-old female is transferred from a nursing home for failure to thrive as a result of decreased oral intake. A nasogastric tube is placed via the left nares for enteral hyperalimentation
- One week into her hospital course, the patient develops fever to 101.5° F, and left periorbital edema and chemosis
- CT scan of the head without contrast reveals opacification of the sphenoid sinus

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD



Question #4 (CASE #7) PREVIEW QUESTION

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

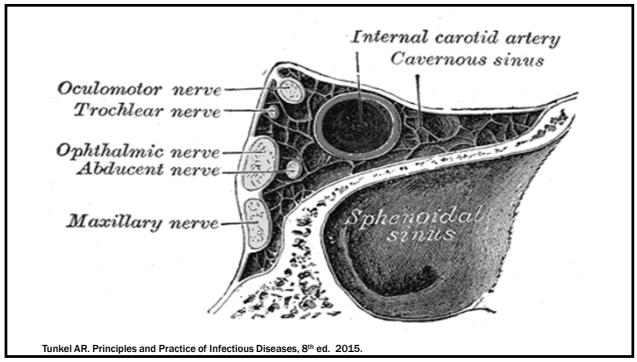
A. CT scan of the head and sinuses with contrast
B. MR imaging with MR venography
C. Cerebral angiography
D. Positron emission tomography of the head
E. Lumbar puncture

EPIDEMIOLOGY AND ETIOLOGY OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Risk Factors	Etiologic Agents
Paranasal sinusitis	Staphylococci (60-70%)
Facial infection	Streptococci (~17%)
Dental infection	Gram-negative bacilli (~5%)
	Pneumococci (~5%)
	Bacteroides sp. (~2%)

CLINICAL FEATURES OF SEPTIC CAVERNOUS SINUS THROMBOSIS

Symptoms	Signs
Headache (52%)	Periorbital edema (73%)
Facial pain	Chemosis
Vision loss	Papillitis
Fever	Oculomotor palsies
Double vision	Proptosis



Tunkel AR. Principles and Practice of Infectious Diseases. 8th ed. 2015.

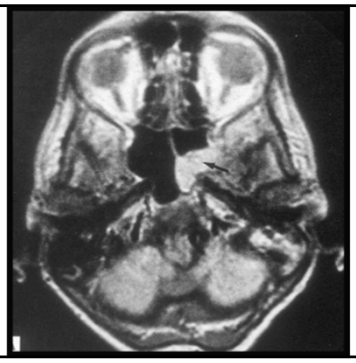
RADIOLOGIC FINDINGS IN SEPTIC CAVERNOUS SINUS THROMBOSIS

MR imaging

- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

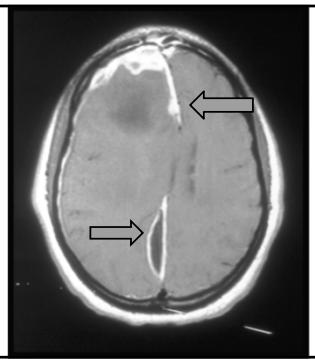


MANAGEMENT OF SEPTIC CAVERNOUS SINUS THROMBOSIS

- Culture and drainage of infected sinuses
- Antimicrobial therapy (vancomycin + metronidazole + 3rd or 4th generation cephalosporin)
- Anticoagulation
  - Cavernous sinus thrombosis
  - Lateral sinus thrombosis?
  - Superior sagittal sinus thrombosis?

CASE #8

- 22-year-old man with a history of paranasal sinusitis presents with fever, severe headache, neck pain, and seizure
- On physical examination, T 102° F and he is lethargic
- Laboratory studies normal



Question #5 (CASE #8)

In addition to appropriate antimicrobial therapy, what other management should be performed?

A. Lumbar puncture
B. External ventricular drain
C. Dexamethasone
D. Burr hole drainage
E. Craniotomy

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Risk Factors	Etiologic Agents
Sinusitis (50-80%)	Staphylococci (10-15%)
Otogenic	Streptococci (25-45%)
Head trauma	Gram-negative bacilli (3-10%)
Neurosurgery	Other anaerobes (8%)
Hematogenous	Others (8%)
Meningitis	Unknown (20%)

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CRANIAL SUBDURAL EMPYEMA AND CRANIAL EPIDURAL ABSCESS

Subdural Empyema (acute course)	Epidural Abscess (indolent course)
▫ Fever	▫ Headache
▫ Headache	▫ Fever
▫ Depressed consciousness	▫ Seizures
▫ Hemiparesis	▫ Focal neurologic signs
▫ Seizures	▫ Altered mental state
▫ Nuchal rigidity	
▫ Gaze palsies/ataxia	

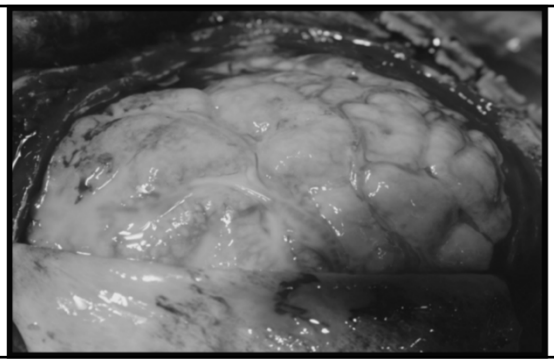
PRINCIPLES OF MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

- MR imaging (diagnostic procedure of choice) provides better clarity of detail and can differentiate empyema from most sterile effusions and chronic hematomas; diffusion-weighted imaging adds to value of MRI
- Surgical therapy (burr holes or craniotomy) is imperative; better outcome with craniotomy
- Empiric antimicrobial therapy based on pathogenesis of infection

SURGICAL MANAGEMENT OF CRANIAL SUBDURAL EMPYEMA

Surgical Procedure	Mortality Rate
Burr hole(s)	23.3%
Craniectomy	11.5%
Craniotomy	8.4%

Nathoo et al. Neurosurgery 2001;49:872



EPIDEMIOLOGY OF SPINAL EPIDURAL ABSCESS

- Usually occurs secondary to hematogenous dissemination (~50% of cases)
- Contiguous foci (~1/3rd of cases)
- Unidentified source (20-40% of cases)
- Diabetes mellitus identified in up to 50% of patients

ETIOLOGY OF SPINAL EPIDURAL ABSCESS

Organism	Relative Frequency (%)
Staphylococci	50-90
Streptococci	8-17
Gram-negative bacilli	12-17
Other anaerobes	2
Other	2
> 1 organism	5-10
Unknown	6

33 – Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Speaker: Allan Tunkel, MD

CLINICAL STAGES OF SPINAL EPIDURAL ABSCESS

I. Back pain and tenderness at the level of infection
II. Radicular pain and paresthesias
III. Impaired spinal cord function; motor paresis and sensory deficits
IV. Complete paralysis

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- MR imaging is the diagnostic procedure of choice; can visualize the spinal cord and epidural space, and can identify accompanying osteomyelitis, intramedullary spinal cord lesions, and joint space infection
- Empiric antimicrobial therapy should include an antistaphylococcal agent and coverage for gram-negative bacilli

PRINCIPLES OF MANAGEMENT OF SPINAL EPIDURAL ABSCESS

- Surgical therapy imperative in the presence of neurologic dysfunction (best if <24-36 hours of complete paralysis)
- Nonsurgical therapy only for patients with an unacceptably high surgical risk or no neurologic deficits at diagnosis; patient must be followed carefully for clinical deterioration

58 **QUESTIONS**

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