VOLUME 2

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30th Annual

COMPREHENSIVE REVIEW *for* INFECTIOUS DISEASE BOARD PREPARATION

www.IDBoardReview.com

GW | Office of Continuing Education in the Health Professions

IDBR
INFECTIOUS DISEASE BOARD REVIEW
AUGUST 16-20, 2025

TABLE OF CONTENTS – VOLUME 2

COURSE OVERVIEW

ABOUT THE COURSE

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

The IDBR course is developed not only to expand your knowledge, but also to help you find areas in which you need to increase your knowledge. Neither the lectures nor the review questions cover all the topics that may be on the ABIM exam. The review questions during the live/virtual, and on-demand courses should give you a better idea of the format and depth of detail you can expect from the ABIM exam. You can compare your scores with other registrants. Now that the Maintenance of Certification (MOC) exam allows access to “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 a question from the IDBR Question Sets, the correct answer and rationale are provided, so users will know if their search produced the needed information. As the exam is time-limited, we anticipate that searching “Up-to-date” will need to be focused and limited. The certifying exam does not provide “Up-to-date” access.

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

EDUCATIONAL OBJECTIVES

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

PROGRAM FACILITATORS

The Infectious Disease Board Review Course
Phone: (301) 818-6754
Email: info@idboardreview.com

CME PROVIDER

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

ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

TYPES OF CREDIT

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

- Attending the Live/Virtual Course - 43.50 credits
- Completing the Online Materials - 73.25 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 43.50 *AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CLAIMING MOC POINTS

Successful completion of this CME activity enables the participant to earn up to 43.50 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

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

DEADLINE FOR CLAIMING MOC POINTS

ABIM Board Certified physicians need to claim MOC points for this course by December 31, 2025 in order for the MOC points to count toward any MOC requirements that are due by the end of 2025.

CEHP will continue to submit participant completion data for the course until August 20, 2026. No ABIM MOC credit will be awarded for this activity after August 20, 2026.

OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

LIVE MATERIALS

LIVE LECTURES
• 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 7th 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.
TO CLAIM CME CREDIT(S): • Complete the five (5) daily session/speaker evaluations (emailed at the end of each day). • Complete the final course evaluation (emailed on the final day of the course). • Upon completing the final course evaluation, you will be redirected to the link to claim CME credit where you will be asked to check the Attestation Statement box and enter the number of CME credits commensurate with the extent of your participation in the activity.
TO CLAIM MOC POINT(S): • You must pass the Pre-/Post- Tests to claim MOC points. • You will be asked to attest whether you want your participation in the live/virtual course to be reported to the ABIM. • Be sure to update your name, ABIM number, and date of birth in your IDBR Course account.

ONLINE MATERIALS

ACCREDITATION

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

CME CREDIT FOR PHYSICIANS

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 73.25 *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 73.25 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

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

CLAIMING MOC POINTS

Participants can earn up to 73.25 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, 2025 in order for the MOC points to count toward any MOC requirements that are due by the end of 2025.

CEHP will continue to submit participant completion data for the course until August 20, 2026. No ABIM MOC credit will be awarded for this activity after August 20, 2026.

OVERVIEW OF ONLINE MATERIALS

CLAIMING CME AND MOC

ONLINE ONLY LECTURES	CME HOURS: 7.25	MOC POINTS: 7.25
• These lectures feature topics that were not covered in the live/virtual course.		
QUESTION SETS	**CME HOURS: 56**	**MOC POINTS: 56**
• There are four (4) sets of 100 board prep questions. • There is one (1) set of 100 photo opportunity questions. • There is one (1) set of 40 HIV Therapy questions. • You will see the correct answer and rationale after submitting each question. • You can only go in the forward direction when answering questions. • You cannot go backwards, but you can retake each set of questions as many times as you like.		
PRIMERS AND STUDY GUIDES	**CME HOURS: 10**	**MOC POINTS: 10**
• There are eight (8) study guides and primers that present core material for you to review. • This PDF reviews information that summarizes important topics in photos, tables and short summaries.		

GUIDE TO ONLINE MATERIALS ACCESS

Initial Notification

- If you registered on or before June 14, 2025, you should have received an email confirmation from info@idboardreview.com before or on June 15 with information on accessing the online materials.
- If you register after June 15, 2025, you will receive the access information included in the registration confirmation email.

Current Access

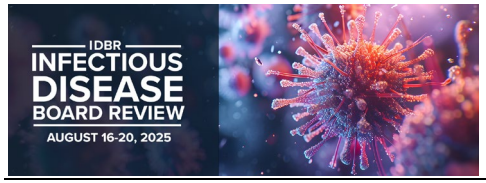
Instructions for accessing the Online Materials:

- Course Page: https://cme.idboardreview.org/content/2025-infectious-disease-board-review-course
- Go to the course enrollment page.
- Click **REGISTER** under the course module titles.
- Complete all required profile fields (marked with a red asterisk*).
- Click "Create New Account."
- Once your account has been created, enter access code **25IDBRLV**
- Click the "Unlock" button.
- Click the "Enroll" button.
- Select one of the course materials to begin studying.

Important Links

Please note that you must be logged in to access.

- Main Course Link: https://cme.idboardreview.org/content/2025-infectious-disease-board-review-course
- To Edit Your User Profile: https://cme.idboardreview.org/user/login?destination=my/edit/profile
- To View/Download Your CME Certificate After Completing the Course: https://cme.idboardreview.org/user/login?destination=my/activities
- To View the List of Course Activities: https://cme.idboardreview.org/user/login?destination=my/activities/pending

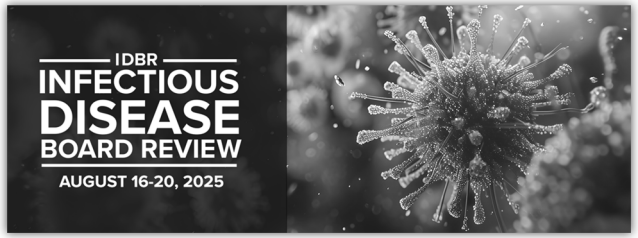


Pre-Test

Please complete this test online at https://cme.idboardreview.org/idbr25/

Instructions: *Completion of the Pre-Test is required to earn CME and MOC. Please review the following before you begin:*

- *You may only take the Pre-Test once.*
- *There is no passing score required.*
- *After each question you will see whether your answer was correct or incorrect.*
- *The correct answers and explanations will be provided upon completion of the Post-Test, after the live course has ended.*



Pre-Test

7/22/2025

1

PRE-TEST

#1 **For a 25-year-old MSM with HIV infection (CD4 375cells/mm3 with VL < 50 copies/uL), who received all recommended pediatric vaccines many years prior to his HIV diagnosis.**

He had an episode of dermatomal herpes zoster when he was 19 years old but was not tested for HIV until several years later despite being at risk due to his sexual activity.

What would you recommend regarding zoster vaccine (Shingrix)?

A. As with HIV uninfected persons, he should receive zoster vaccine when he is age 65 years

B. He does not need zoster vaccine because of his prior episode of zoster

C. Zoster vaccine is contraindicated in any person with HIV

D. He should receive zoster vaccine (Shingrix) now

2

PRE-TEST

#2 **A 60-yr old woman has had repeated episodes of erysipelas in her left arm after breast surgery and radiation for cancer had caused substantial lymphedema in that arm. She has inquired whether you might prescribe something she could take to prevent these infections. She has no history of drug allergies or intolerance.**

Among the options you discuss with her might include taking which of these antibiotics prophylactically?

A. Trimethoprim-sulfamethoxazole

B. Penicillin V

C. Clindamycin

D. Amoxicillin-clavulanate

E. Erythromycin

3

PRE-TEST

#3 **A 34-year-old man is admitted with 3 weeks of intermittent fevers, productive cough, and a 15lb weight loss.**

He was born in Guatemala but has been living in the US for the past 12 years.

He is married and has two kids, ages 6 and 8. All family members are healthy.

Workup is significant for fever (temp 38.2 C), mild tachypnea (respiratory rate 24 breaths per minute), mild hypoxemia (oxygen saturation 93% on ambient air), and cavitary lesion in the right upper lobe.

HIV test is negative.

4

PRE-TEST

#3

Sputum gram stain and culture are unrevealing.

Sputum AFB smear is negative but tuberculosis nucleic acid amplification on the sputum is positive.

He's started on empiric treatment with isoniazid, rifampin, pyrazinamide, and ethambutol.

When can this patient be discharged home?

A. Immediately

B. As soon as sputum cultures confirm drug susceptible tuberculosis

C. After symptom improvement and a minimum of one week of active treatment

D. After a minimum of two weeks of active treatment

5

PRE-TEST

#4

A 24-year-old woman presents to the emergency department with two days of high fever, profound fatigue, and cough.

She was previously healthy and has lived in the US all of her life in an isolated religious community which did not immunize its children or adults.

Review of systems is notable for conjunctivitis and nasal congestion but no shortness of breath, abdominal pain, diarrhea, or rash.

She returned one week ago from a trip to Bosnia and Herzegovina with a church group.

6

PRE-TEST

#4

While abroad she did volunteer work in a school, went hiking in the mountains, stayed on a farm, helped to milk cows, and drank unpasteurized milk.

On exam she looks unwell, temperature is 103 degrees Fahrenheit, heart rate is 110 beats per minute, blood pressure is 100/70mm Hg, respiratory rate is 24 breaths per minute, oxygen saturation is 94% on ambient air.

Exam is notable for conjunctival infection but is otherwise normal. She has no rash.

Chest x-ray is normal. Nasopharyngeal swab is negative for influenza, RSV, and SARS-CoV-2 by PCR.

7

PRE-TEST

#4

What precautions if any will you implement for this patient in the Emergency Department or in the hospital if she were to be admitted?

A. Airborne

B. Droplet

C. Contact

D. Contact + Droplet

E. Contact + Airborne

8

PRE-TEST

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

The patient also has cryptosporidiosis with 6 stools per day plus considerable nausea and thus has limited food intake.

The pharmacy cannot obtain sulfadiazine or pyrimethamine.

What would be the best option for toxoplasmosis therapy?

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

9

PRE-TEST

#6 Which of the following is correct regarding primary prophylaxis for disseminated mycobacterium avium complex (MAC) disease?

A. Initiate primary prophylaxis if CD4 count is <50 cells/mm^3
B. Initiate primary prophylaxis if CD4 count is <100 cells/mm^3
C. Initiate primary prophylaxis if CD4 count is <200 cells/mm^3
D. Primary prophylaxis is not recommended for people with HIV who immediately initiate antiretroviral therapy

10

PRE-TEST

#7 A person with HIV who takes antiretroviral therapy as prescribed and achieves and maintains viral suppression will not transmit HIV to their sex partners (Undetectable = Untransmittable).

Viral suppression in the context of treatment as prevention is defined by the Centers for Disease Control and Prevention as?

A. HIV-RNA level below the lower limit of detection of available assay
B. HIV-RNA level < 50 copies/mL
C. HIV-RNA level < 200 copies/mL
D. HIV-RNA level < 1000 copies/mL

11

PRE-TEST

#8 A 69-year-old female was seen because the nurse noted a new skin lesion. The patient was hospitalized for fever, found due to Candia parapsilosis bacteremia, treated with caspofungin for the last three days.

She was day 87 post allogeneic stem cell transplant with chronic graft versus host disease causing colitis, for which she was receiving prednisone 60 mg, sirolimus, daclizumab and rituximab.

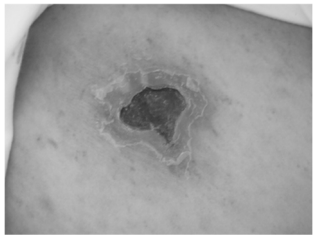
She was also receiving filgrastim for chronic neutropenia (WBC 11600. ANC 1000). One exam, she complained of fatigue and was not aware of six skin lesions on her extremities and abdomen.

Vital signs were temp 37.4C, pulse 121, BP 106/67.

12

PRE-TEST

#8



Which is the most likely cause of skin lesions?

A. Ecthyma gangrenosum
B. Pyoderma gangrenosum
C. Sweet syndrome
D. Disseminated herpes zoster
E. Nontuberculous mycobacteriosis

13

PRE-TEST

#9

A 23-year-old man presented to the emergency department with 18 days of severe sore throat, not improving despite injection of ceftriaxone and a course of azithromycin given him in emergency room visits 2 and 14 days prior.

Rapid strep tests on a throat swab had been negative at prior visits.

In addition, four pustular lesions had appeared in the prior two days, scattered over his trunk and extremities. He felt feverish at night but had not taken his temperature.

He lived in downtown Washinton DC, worked in retail, had sex with men and had no recent travel, medications, or illicit drugs.

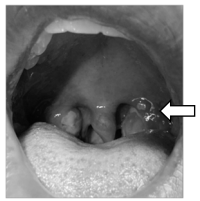
On exam, he had severe tonsilitis, temperature of 38.5C, prominent submental lymph nodes and four skin lesions like the one shown below.

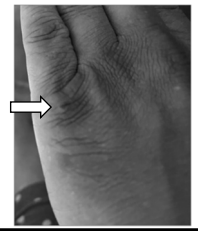
His routine labs were normal.

14

PRE-TEST

#9





Which of the following is most likely to be useful?

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

15

PRE-TEST

#10

A 78-year-old woman is admitted to hospital with 2 months of progressive weakness, fatigue, shortness of breath, and 10 lb weight loss.

She has a history of non-Hodgkins lymphoma that was treated 20 years ago with radiation and chemotherapy.

Workup is notable for bilateral, patchy, upper lobe predominant infiltrates on chest CT.

Bronchoscopy gram stain and culture are unrevealing but AFB smear is positive and a tuberculosis nucleic acid amplification test is positive.

She's placed on Airborne precautions, moved to an Airborne Infection Isolation Room (AIIR), and started on standard 4-drug anti-tuberculous therapy.

16

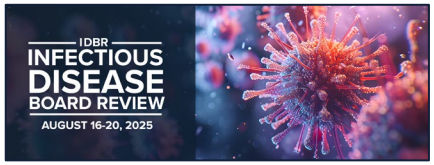
PRE-TEST

#10 **She has multiple complications unrelated to her tuberculosis and thus must stay on the rehabilitation service.**

The team calls and asks when can she come off airborne precautions?

A. **Immediately –she does not need isolation in the hospital**
B. **As soon as her symptoms are clearly improving**
C. **After a minimum of two weeks of active therapy**
D. **After at least three consecutive AFB smears collected ≥ 8 hours apart are negative**
E. **After a minimum 2 weeks active therapy, symptom improvement, and 3 negative sputum AFB smears**

17



Agenda Day 4: Tuesday, August 19, 2025

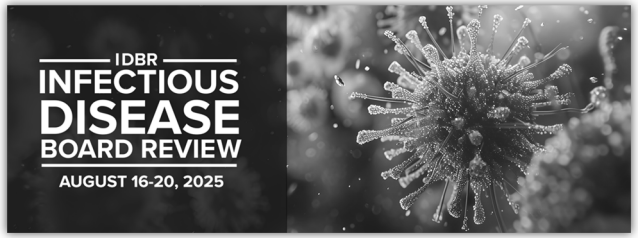
#	Start		End	Presentation	Faculty
AM Moderator: Roy Gulick, MD					
QP4	8:00 AM EDT	-	8:30 AM EDT	Daily Question Preview Day 4	Roy Gulick, MD
33	8:30 AM	-	9:15 AM	Clinical Manifestations of Human Retroviral Diseases and Slow Viruses	Frank Maldarelli, MD
34	9:15 AM	-	10:00 AM	HIV-Associated Opportunistic Infections I	Henry Masur, MD
35	10:00 AM	-	10:15 AM	HIV Diagnosis	Frank Maldarelli, MD
	10:15 AM	-	10:30 AM	Morning Break	
36	10:30 AM	-	11:15 AM	Antiretroviral Therapy	Roy Gulick, MD
37	11:15 AM	-	11:30 AM	HIV Drug Resistance	Michael Saag, MD
38	11:30 AM	-	12:15 PM	Antiretroviral Therapy for Special Populations	Roy Gulick, MD
	12:15 PM	-	12:45 PM	Lunch Break	
PM Moderator: Roy Gulick, MD					
BR4	12:45 PM	-	1:30 PM	Board Review Day 4	Drs. Gulick (Moderator), Bloch, Gandhi, Maldarelli, Masur, Saag, and Tunkel
39	1:30 PM	-	1:45 PM	Pharyngitis Syndromes Including Group A Strep Pharyngitis	Karen Bloch, MD
40	1:45 PM	-	2:30 PM	HIV-Associated Opportunistic Infections II	Rajesh Gandhi, MD
41	2:30 PM	-	3:15 PM	Syndromes Masquerading as Infections	Karen Bloch, MD
	3:15 PM	-	3:30 PM	Afternoon Break	
42	3:30 PM	-	4:15 PM	Non-AIDS-Defining Complications of HIV/AIDS	Michael Saag, MD
43	4:15 PM	-	5:00 PM	Bacterial and Viral Meningitis	Allan Tunkel, MD
44	5:00 PM	-	5:45 PM	Photo Opportunity I: Photos and Questions to Test Your Board Preparation	Rajesh Gandhi, MD
45	5:45 PM	-	6:30 PM	Herpes Simplex	Richard Whitley, MD

Tuesday, August 19, 2025

QP4

Daily Question Preview 4

Roy Gulick, MD



Daily Question Preview: Day 4

Moderator: Roy Gulick, MD, MPH

7/22/2025

1

PREVIEW QUESTION

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

A. Disseminated histoplasmosis
B. Cryptococcal meningitis
C. Coccidiodes meningitis
D. Miliary tuberculosis
E. Disseminated Mycobacterium avium complex

1 of 2

2

PREVIEW QUESTION

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

Do you recommend starting ART?

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

1 of 2

3

PREVIEW QUESTION

4.3 **25-year-old man presents with newly diagnosed HIV**
Had an episode c/w acute seroconversion syndrome 4 months ago
Initial HIV RNA 40,000; CD4 443 cells/ul
He wants to start ARV therapy
A baseline genotype is ordered that shows an M184V mutation.

Which of the following drugs will have reduced susceptibility with this mutation?

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

1 of 2

4

QP4 Daily Question Preview-Day 4
Moderator: Roy Gulick, MD, MPH

PREVIEW QUESTION

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

Which statement is correct?

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

1 of 2

5

PREVIEW QUESTION

4.5 50-year-old woman with HIV (CD4 20, HIV RNA 500,000) presents with fever and headache. Not on antiretroviral therapy (ART). Diagnosed with cryptococcal meningitis

Started on induction therapy (liposomal amphotericin plus 5FC)

When should she be started on ART?

A. Start ART at the same time as anti-fungal therapy
B. About 4 weeks after starting anti-fungal therapy
C. 6 months after starting anti-fungal therapy
D. After completing a full course of maintenance anti-fungal therapy

1 of 2

6

PREVIEW QUESTION

4.6 45-yo man with HIV (CD4 11, HIV RNA 300,000) presents with fever, diarrhea and weight loss.
Started on dolutegravir + tenofovir/emtricitabine
Two weeks later, develops enlarged supraclavicular lymph node
Biopsy: necrotizing granulomas and AFB; cultures grow MAC

What would you recommend?

A. Stop ART and initiate treatment for MAC
B. Continue ART; initiate treatment for MAC
C. Start steroids and stop all other treatments

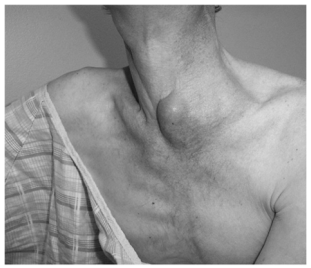


Image from Riddell J, J Translational Med, 2007

1 of 2

7

PREVIEW QUESTION

4.7 A 19-year-old Iraqi immigrant is hospitalized for 2-day history of fever and abdominal pain.

He has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the appendix path was normal. Subsequent episodes resolved spontaneously after 2-3 days.

Exam:

T 102.2; pulse 114; no rash

Abdominal guarding, rebound tenderness, hypoactive bowel sounds

Labs:

WBC 16,650; UA normal

BMP & LFTs normal

No occult blood in stool

CT of abdomen and pelvis normal

1 of 3

8

QP4 Daily Question Preview-Day 4

Moderator: Roy Gulick, MD, MPH

PREVIEW QUESTION

4.7 **What is the most likely diagnosis?**

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

2 of 3

9

PREVIEW QUESTION

4.8 A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats.

He has had nasal stuffiness for 4-5 months with occasional epistaxis.

He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business.

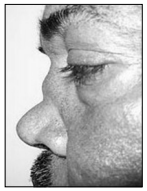
He has no pets and takes only an OTC decongestant. He denies use of illicit substances, including intranasal cocaine.

1 of 4

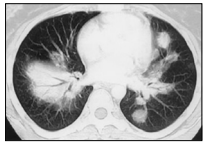
10

PREVIEW QUESTION

4.8 Exam:
T 100.2; RR 18;
Nasal deformity with perforation of septum
Lungs clear; rest of exam normal



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



2 of 4

11

PREVIEW QUESTION

4.8 **Which of the following will most likely support the diagnosis?**

A. c-ANCA
B. Anti-glomerular basement membrane Ab
C. Urine toxicology screen
D. Angiotensin converting enzyme (ACE)
E. Pulmonary angiogram

3 of 4

12

QP4 Daily Question Preview-Day 4
Moderator: Roy Gulick, MD, MPH

PREVIEW QUESTION

4.9 **55-year-old man presents with R hip pain**

H/O COPD requiring steroids frequently

HIV diagnosed 17 years ago

On TDF / FTC / EFV for 10 years; originally on IND / AZT / 3TC

Initial HIV RNA 340,000; CD4 43 cells/ul

Now HIV RNA < 50 c/ml; CD4 385 cells/ul

Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5

Mg 2.1, alk phos 130; U/A neg

R Hip film unremarkable

1 of 3

13

PREVIEW QUESTION

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

A. Osteonecrosis of femoral head
B. Fanconi's syndrome
C. Vitamin D deficiency
D. Tenofovir bone disease
E. Hypogonadism

2 of 3

14

PREVIEW QUESTION

4.10 **35-year-old man presents with complaints of increasing fatigue, headache, SOB / DOE**

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

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

Claims adherence to all meds; "Doesn't miss a dose!"

Normal PE

Pulse Ox 85%; CXR no abnormalities

ABG: 7.40 / 38 / 94/ 96% (room air)

1 of 3

15

PREVIEW QUESTION

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

A. Recurrent PCP
B. IRIS reaction
C. Drug toxicity
D. Pulmonary embolus
E. Patent foramen ovale

2 of 3

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PREVIEW QUESTION

4.11 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 99.8°F 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/mm3 (100% lymphs), glucose of 60 mg/dL, and protein of 100 mg/dL; Gram stain negative

1 of 3

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PREVIEW QUESTION

4.11 Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Parvovirus B19
D. Herpes simplex virus type 2
E. Human herpesvirus 6

2 of 3

18

PREVIEW QUESTION

4.12 A 30-year-old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive despite high-dose intravenous therapy.

Instead of healing, as shown a previous slide, the lesions progress despite antiviral therapy.

A deficiency or alteration of which of the following is the most likely cause for disease progression?

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

1 of 2

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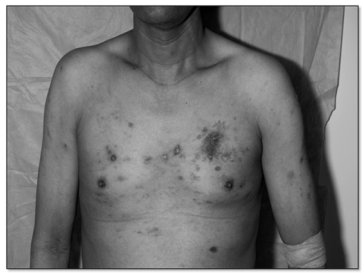
PREVIEW QUESTION

4.13 A patient who was recently found to be HIV positive…

- (CD4=10 cells/uL, VL=2 mil copies)

Has noted the lesions shown on the following PowerPoint developing on his trunk, face and extremities over the past 8 months.

Otherwise, he felt fine.



1 of 3

20

QP4 Daily Question Preview-Day 4

Moderator: Roy Gulick, MD, MPH

PREVIEW QUESTION

4.13 **What would you expect to be causative agent for these lesions?**

A. HHV-6
B. HHV-8
C. EBV
D. JC Virus
E. BK Virus

2 of 3

21

PREVIEW QUESTION

4.14 **A 26-year-old woman with HIV on TAF/emtricitabine + efavirenz with CD4 630 and VL suppressed below detection becomes pregnant.**

What do you recommend regarding ART?

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

1 of 2

22

PREVIEW QUESTION

4.15 **A 32-year-old woman is seen for a bad sore throat for 4 days**

Recently returned from her sister's wedding in Kazakhstan

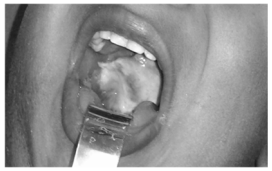
She c/o odynophagia and a low-grade fever

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

HEENT: Submandibular swelling with gray exudate coating posterior pharynx.

An S3 gallop is heard.

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



1 of 3

23

PREVIEW QUESTION

4.15 **What is the most likely diagnosis?**

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

2 of 3

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QP4 Daily Question Preview-Day 4

Moderator: Roy Gulick, MD, MPH

Tuesday, August 19, 2025

33

Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

Frank Maldarelli, MD

Clinical Manifestations of Human Retroviral Disease and Slow Viruses

Frank Maldarelli, MD
Bethesda, MD

7/25/2025

1

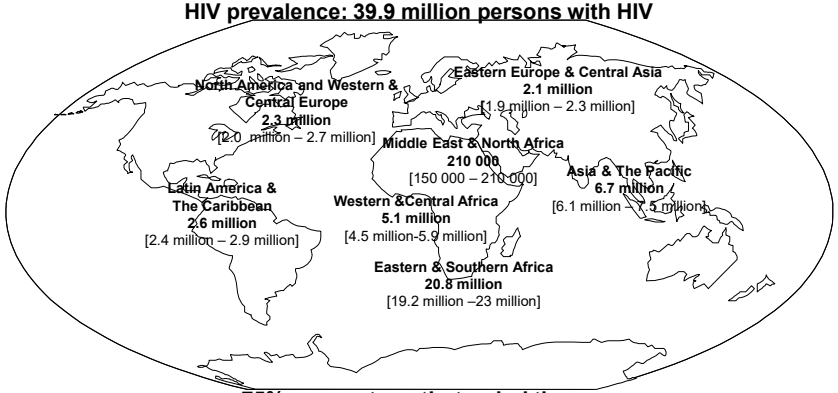
Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or "None"

2

Estimated Numbers of Adults and Children with HIV 2024

HIV prevalence: 39.9 million persons with HIV



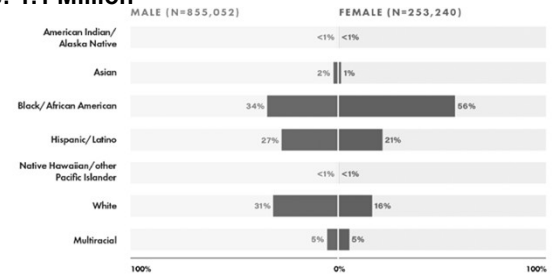
>75% access to antiretroviral therapy
HIV incidence: 1.3 million new infections/year

UNAIDS

3

Current US Epidemic

Prevalence: 1.1 Million



75% Male
70% Persons of Color

Diagnoses: 31,500 in 2023

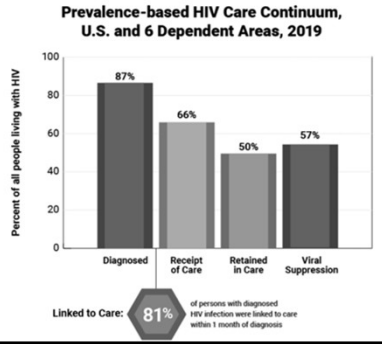
CDC, 2024

Gay, bisexual, and other men who have sex with men	68%
Heterosexual Contact	22%
IDU	10%

4

2030 US HIV Public Health Goals:Treatment Cascade

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



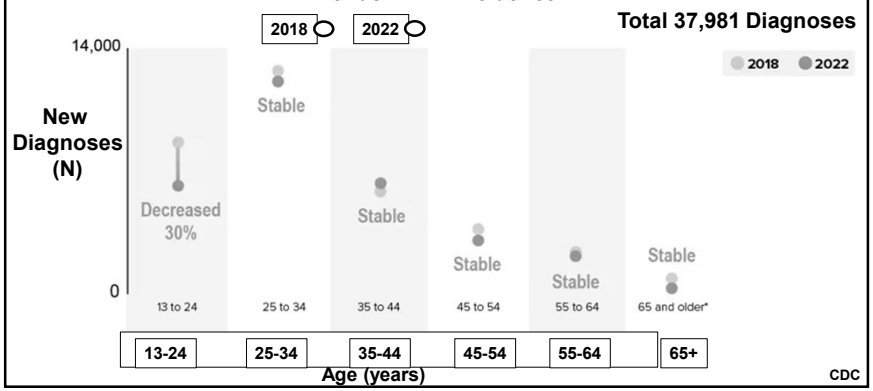
>50% Diagnoses are <35
>50% Living with HIV are>50 years

CDC

5

2030 US HIV Public Health Goals: Transmission

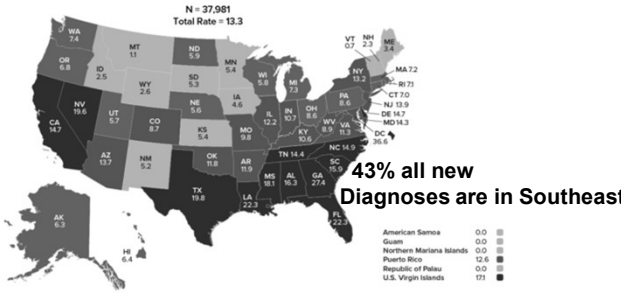
90% Reduction in Incidence by 2030



CDC

6

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

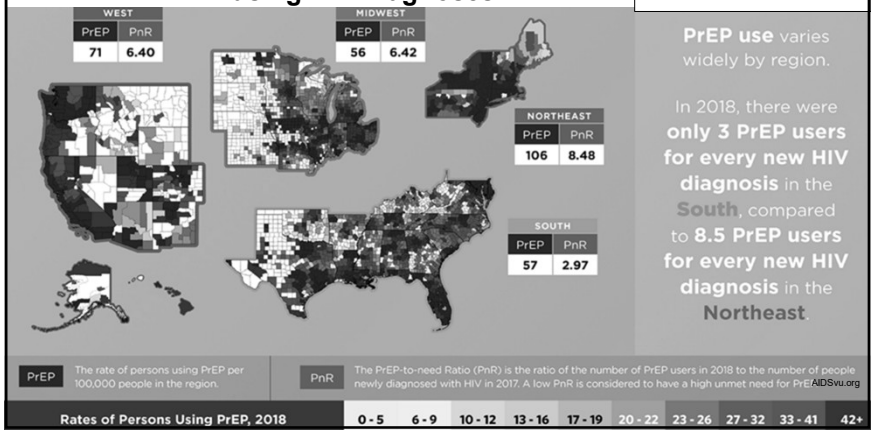


43% all new Diagnoses are in Southeast

Note. 2019 Data. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.
†Total estimate for the United States does not include data for Puerto Rico.

7

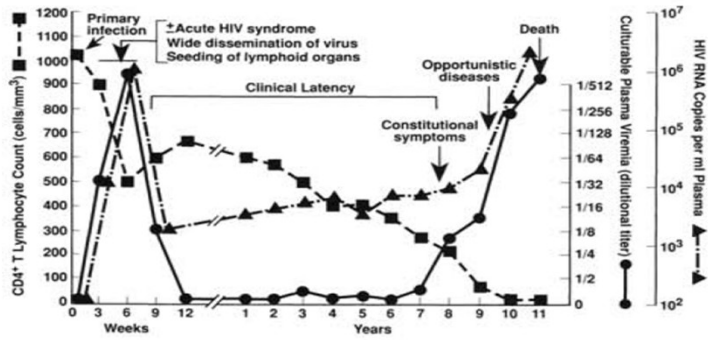
PrEP-to-Need Ratio: PrEP using/HIV Diagnoses



8

33 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses
Speaker: Frank Maldarelli, MD

HIV Infection Course



9

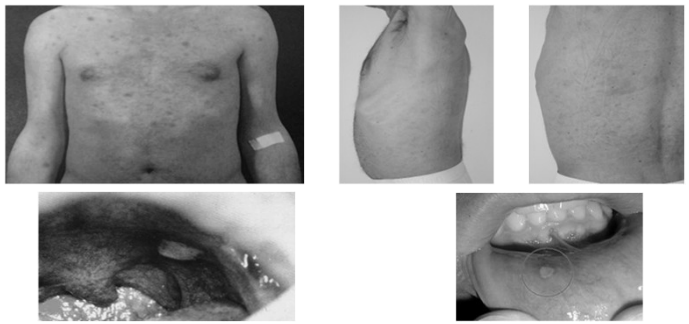
Acute HIV Syndrome

Sign/Symptom	Percent Reporting NEJM Review	Kenyan Sex Workers	HIVNET
Fever	>80-90	53	55
Fatigue	>70-90	26	56
Rash	>40-80	9	16
Headache	32-70	44	33
Lymphadenopathy	40-70	7	35
Pharyngitis	50-70	15	43
Myalgia or arthralgia	50-70	24	39
Nausea, vomiting or diarrhea	30-60	18	12-27
Night sweats	50	nd	nd
Aseptic meningitis	24	nd	nd
Oral ulcers	10-20	nd	6
Genital ulcers	5-15	3	nd
Thrombocytopenia	45	nd	nd
Leukopenia	40	nd	nd
Elevated LFTs	2	nd	nd
Too ill to work	1	44	58

10

Primary HIV-1 Infection Syndrome

Maculopapular Trunk > Extremities



Enanthem *Aphthous ulcer*

11

Question #1

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

ELISA is reactive. HIV-2 assay is negative. Viral RNA on therapy is <40 c/ml.

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Question #1

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

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

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Early Antiretroviral Therapy

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

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Question #2

A 30-year-old individual who is completely adherent with long-acting cabotegravir as PrEP presents in January to your ED with low grade fever, fatigue, and mild myalgias. 4th generation HIV testing is non-reactive, rapid Flu A testing is negative.

15

Question #2

The ER physician asks whether this patient may have breakthrough HIV infection in the setting of PrEP, and whether further evaluation for HIV infection should be arranged.

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

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Long Acting Early Viral Inhibition (LEVI) Syndrome

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

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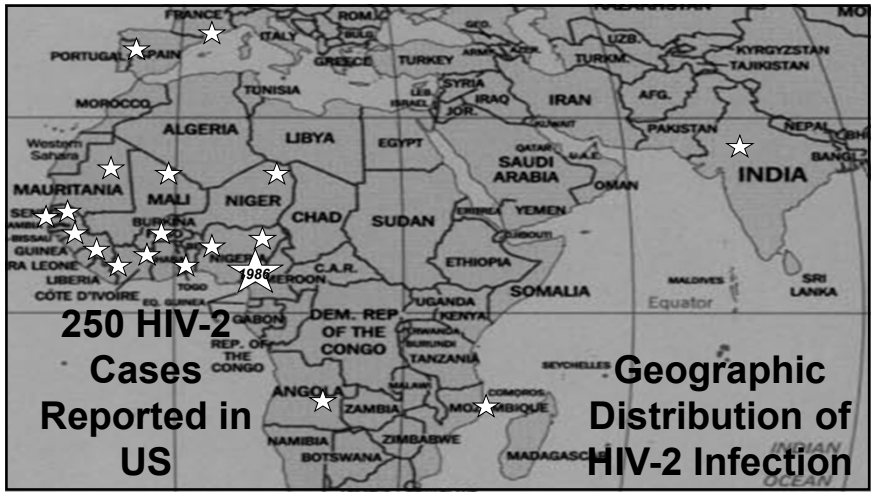
Question #3

A 49-year-old woman from Guinea-Bissau has a reactive HIV-1/2 ELISA and a HIV Geenius positive for HIV-2 and negative for HIV-1. CD4 cell count is 350 cells/μl.

Which of the following is correct?

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

18



19

HIV-1 and HIV-2

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

20

Question #4

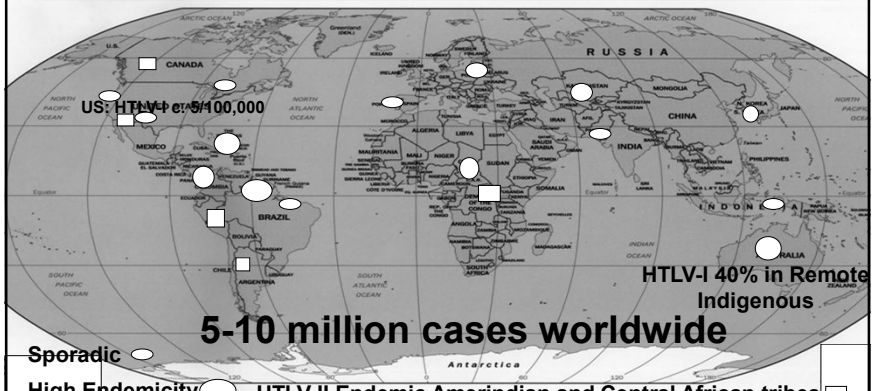
A 25-year-old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot.

Which of the following statements is true?

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

21

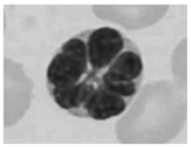
HTLV DISTRIBUTION



22

HTLV-I Transmission, Pathogenesis, Diagnostics

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


Flower cell: HTLV-infected cell

23

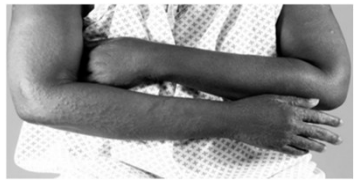
Question #5

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

WBC: 50,000, 90% lymphocytes

Which is most likely cause of her presentation?

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



24

HTLV-I Acute T cell Leukemia (ATL)

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

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Question #6

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

WBC = 7500 cells/µl
CD4 T cell = 1000 cells/µl
CSF cell count: 10 cells/mm3 (lymphocytes)
CSF protein: 75 mg/dl

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Question #6

The etiologic agent associated with this illness is also associated with which of the following?

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

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

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

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HTLV-I TSP/HAM

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

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Therapy of HTLV-I TSP/HAM

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

30

Question #7

62-year-old woman from Jamaica recently diagnosed with multiple sclerosis who is now experiencing her first relapse and has been prescribed a course of natalizumab. She is also HTLV-1 seropositive; she has never had complications from HTLV, and you are consulted regarding treatment during therapy.

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Question #7

Which of the following is most correct?

A. She is at risk for HTLV disease progression and should not be treated with natalizumab
B. She is not at risk for HLTV disease progression and can be treated with natalizumab.
C. She may be treated with natalizumab but should also be treated with antiretroviral therapy to prevent HTLV reactivation.
D. The HTLV serologic test may be false positive in multiple sclerosis, and she should first be tested for HTLV DNA, if she is DNA positive, she should not be treated with natalizumab.

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Question #8

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

33

Question #8

Which of the following is most correct in explaining these findings?

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

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Question #9

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

35

Question #9

Which of the following is most correct?

A. She should not undergo autologous BMT because of reduced overall survival from ATL or other secondary malignancy in the post transplant period
B. She should not undergo autologous BMT because of the high risk of graft failure
C. She can undergo autologous BMT, but she should be treated with antiretroviral therapy from induction, until she recovers her counts (WBC>500 cells/µl)
D. She can undergo autologous BMT; her 3-year survival is equivalent to individuals without HTLV-I infection.

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Pearls

HTLV-1 Infection

- Asymptomatic -95%
- Acute T cell Leukemia
- HAM/TSP
- But also
  - Bronchiectasis
  - Uveitis
  - Rheumatologic syndromes
  - Lymphocytic pneumonitis
  - Infective Dermatitis (pediatric)
- "Flower" cells
  - Lymphocytes with HTLV provirus present
  - Frequency in HIGHER in ATL and HAM/TSP
  - NOT an indication for specific therapy
- No indication for ART

Associated Infections

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

HTLV-II

Not a cause of disease
A distractor

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

37

SLOW VIRUSES

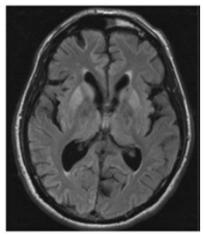
38

Question #10 (Prion Disease)

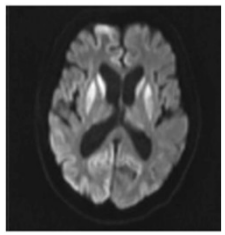
68-year-old butcher who is an avid hunter presents with dementia progressing over 4 months, myoclonus, MRI below, periodic sharp waves on EEG.

What is the most likely cause of the acquisition of this illness?

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



Flair



Diffusion Weighted Image

39

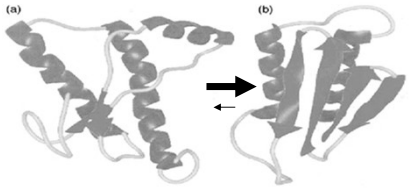
Prion Diseases:
Transmissible Spongiform Encephalopathies

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

40

Prion Disease Pathogenesis
A. Initiation

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



NORMAL ABNORMAL

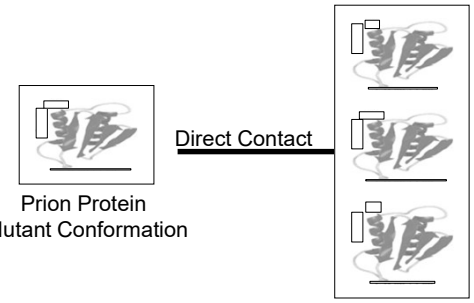
Transition to abnormal conformation is rare but essentially irreversible

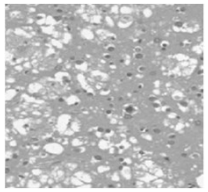
Naturally occurring mutations favor interconversion

41

Prion Disease Pathogenesis
B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation





Disaggregase chaperone proteins may scavenge these proteins with mutant conformation

42

~~Spontaneous Creutzfeldt-Jacob Disease (sCJD)~~ Epidemiology

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

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Dementia Comparison

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

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Question #11 (Prion Disease)

A 68-year-old man with dementia progressing over the last 6 months undergoes evaluation.

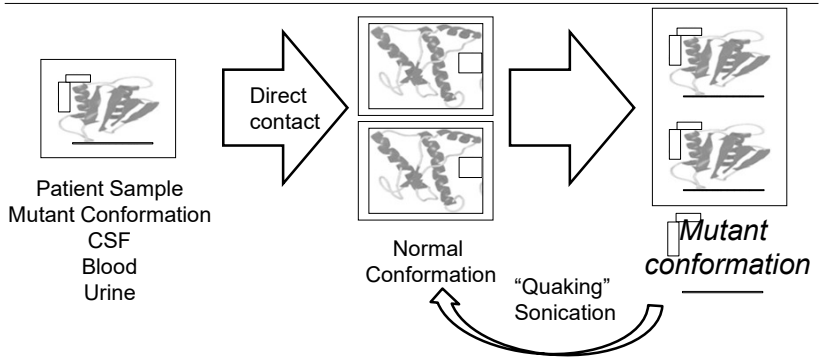
Which of the following CSF results is most consistent with Creutzfeldt Jakob Disease?

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

45

Abnormal Prion Detection

RT-QuIC



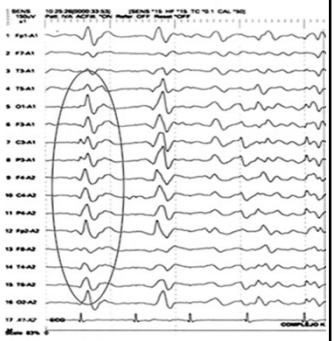
Sensitivity 92% Specificity >99%

46

Spontaneous Creutzfeldt-Jacob Disease (sCJD)

Typical Clinical Presentation

- Rapid progression
- RT-QuIC elevated abnormal prion protein
- Elevated Tau, 14-3-3 are supportive, but not specific for sCJD
- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves



Herran, BMC Neurology 2018

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Question #12 (Prion Disease)

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

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

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

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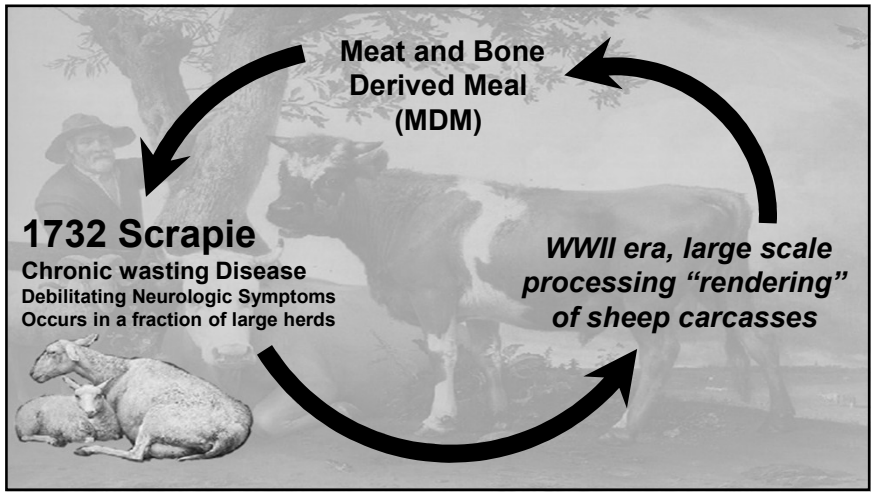
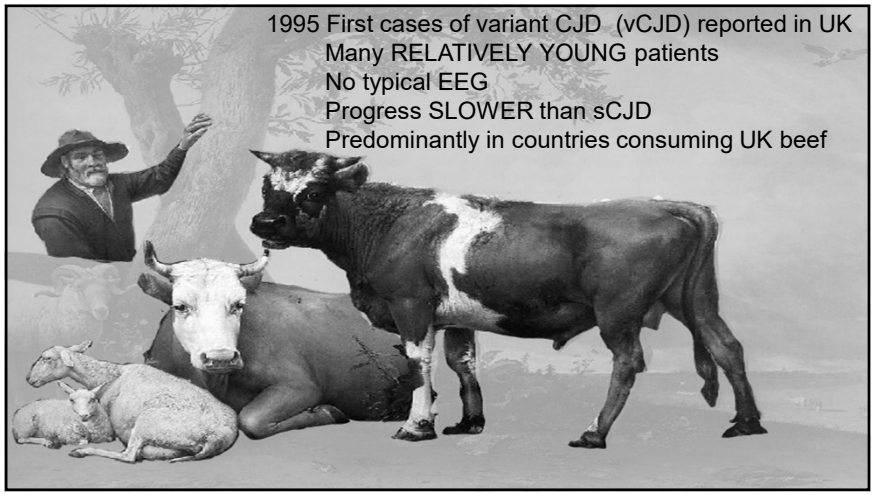
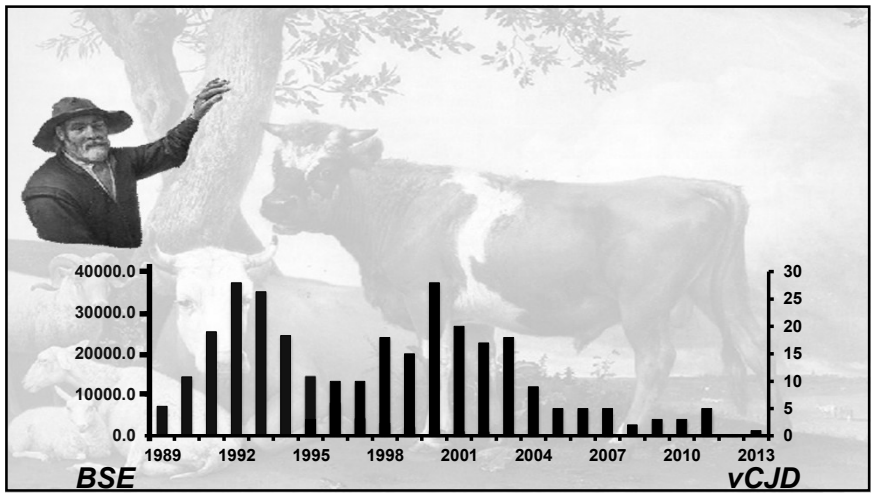


49



50



51

Numbers of vCJD Cases Worldwide

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

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

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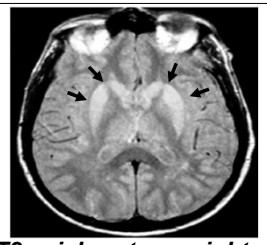
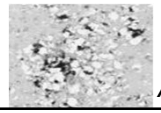
sCJD

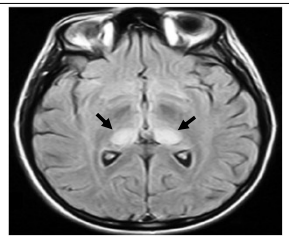


T2 axial proton weighted
Putamen and caudate head
"Double hockey stick sign"

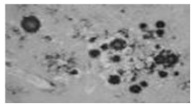


"Abnormal Prion Accumulation"

vCJD



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



"Florid Plaques"

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Question #13 (Prion Disease)

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

What is the most likely cause of his dementia?

A. Iatrogenic CJD from the dura mater graft
B. CJD from eating deer
C. HTLV-I
D. Alzheimer's disease

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Iatrogenic CJD ~450 cases

Definite Causes

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

No Link

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

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CJD and Recommendations

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

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Summary

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

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Prions Reference Material

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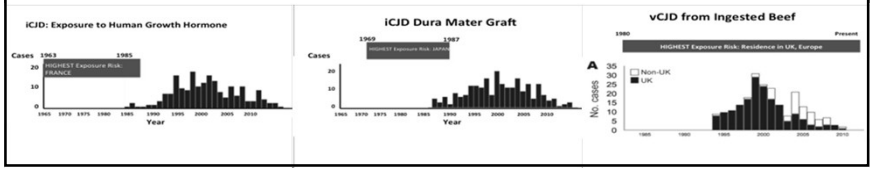
Transmissible Spongiform Encephalopathy: Time and Place

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



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Kuru "Shivering, trembling"

- Fore tribe Papua New Guinea
- Ritual mourning w/cannibalism
- Older females, children (especially female)
- Progressive Ataxia w/dementia
  - Ambulant, leaning (pictured)
  - Sedentary
  - Terminal "laughing death"
  - "Florid plaques" (inset) on H+E
- No maternal/fetal transmission
- New cases would have been infected as children
- No cases <40 y.o. since 1991
- Last recorded case 2009

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CJD and Blood Supply

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

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Transmissible Spongiform Encephalopathy
Infection Control Issues

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

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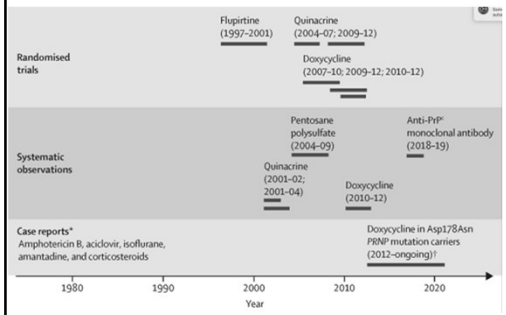
Transmissible Spongiform Encephalopathy
Multiple Trials but NO FDA Approved Therapy



PRN100 Antibody Under Study

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

Future: Disaggregase Induction

Zerr, Lancet Neurology 2022

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Resources

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

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Tuesday, August 19, 2025

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HIV-Associated Opportunistic Infections I

Henry Masur, MD

HIV-Associated Opportunistic Infections I

Henry Masur, MD
Clinical Professor of Medicine
George Washington University School of Medicine

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Question #1

PREVIEW QUESTION

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

A. Disseminated histoplasmosis
B. Cryptococcal meningitis
C. Coccidiodes meningitis
D. Miliary tuberculosis
E. Disseminated Mycobacterium avium complex

3

Question #2

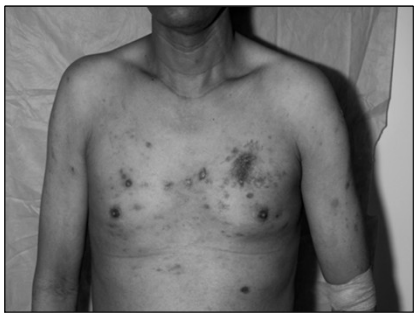
PREVIEW QUESTION

A patient who was recently found to be HIV positive…

- (CD4=10 cells/uL, VL=2 mil copies)

Has noted the lesions shown on the following PowerPoint developing on his trunk, face and extremities over the past 8 months.

Otherwise, he felt fine.



4

Question #2

PREVIEW QUESTION

What would you expect to be causative agent for these lesions?

A. HHV-6
B. HHV-8
C. EBV
D. JC Virus
E. BK Virus

5

Question #3

The patient whose photo is shown:

For your differential diagnosis, what would be the most likely *non-viral* *infectious* cause be the most likely cause of these lesions and their associated fever?

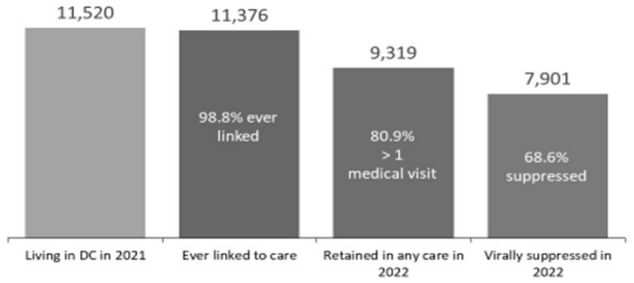
A. Cryptococcus neoformans
B. Blastomyces hominis
C. Treponema pallidum
D. Mycobacterium genevense
E. Bartonella henselae

6

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

7

HIV Care Continuum, Washington DC
2023 Annual Report

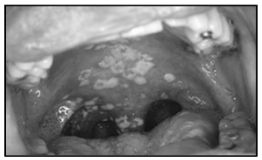


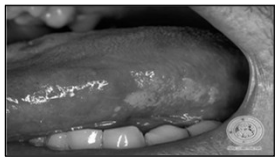
https://dchealth.dc.gov/service/hiv-reports-and-publications

8

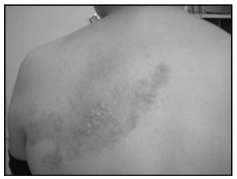
Clinical Indicators of Immunosuppression

Mucosal Candida





Oral Hairy Leukoplakia (EBV)



Dermatomal Zoster

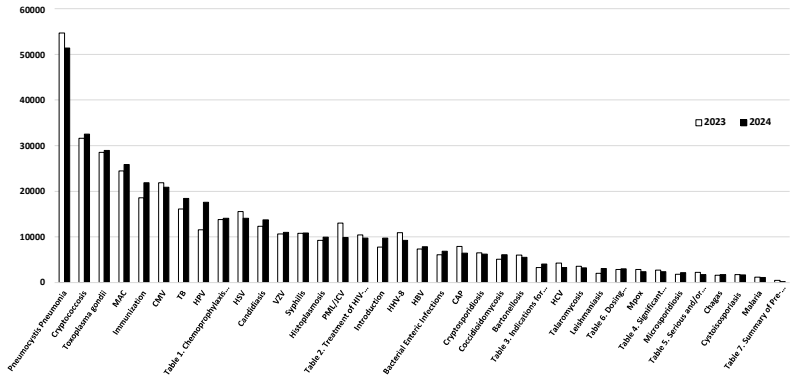
9

Cardinal AIDS-Defining Illnesses

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

10

NIH CDC IDSA HIV Associated Opportunistic Infections Guideline Which Pages Are Consulted Most By Users



11

Susceptibility to Opportunistic Infections Patients with HIV

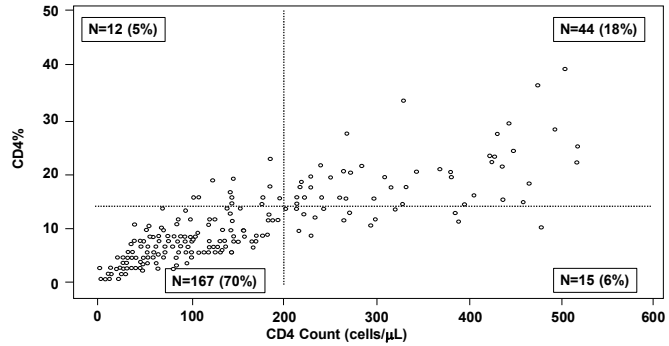
- **CD4 Count**
  - Current count is most important
  - Prior nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

12

At What CD4 Counts Do Opportunistic Infections Occur?

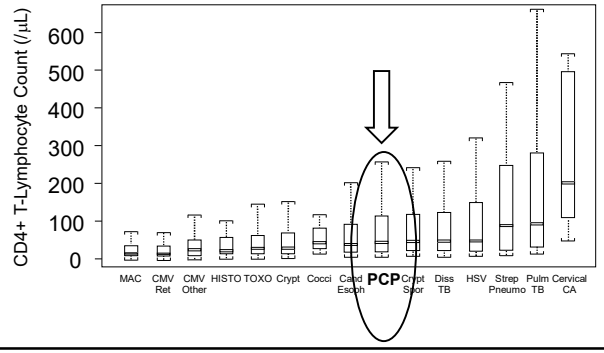
13

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



14

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



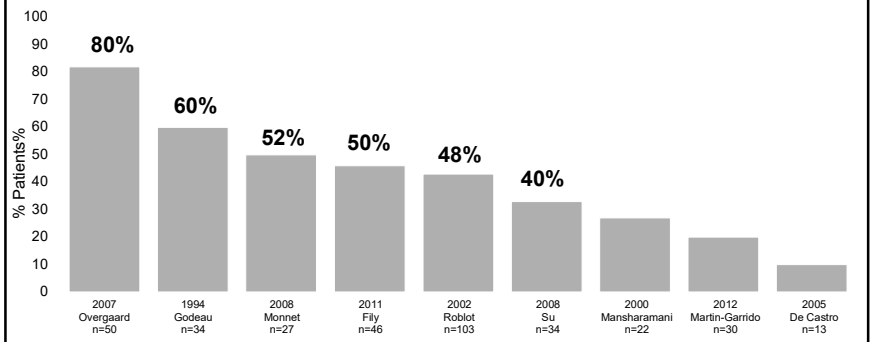
15

Warning for Utility of CD4 Counts in Non-HIV

- CD4 Count Are Not A Useful Indicator of PCP Susceptibility

16

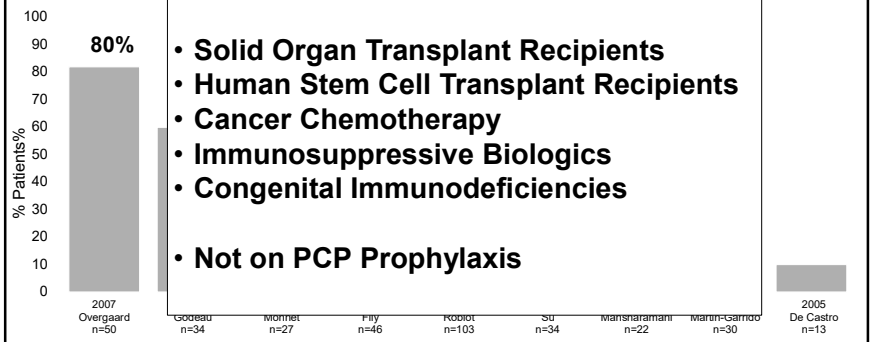
Non-HIV Patients Who Develop PCP When CD4>200



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

17

Non-HIV Patients Who Develop PCP When CD4>200



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

18

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

19

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

Antiretroviral Therapy

20

When to Start ART Following Opportunistic Infection

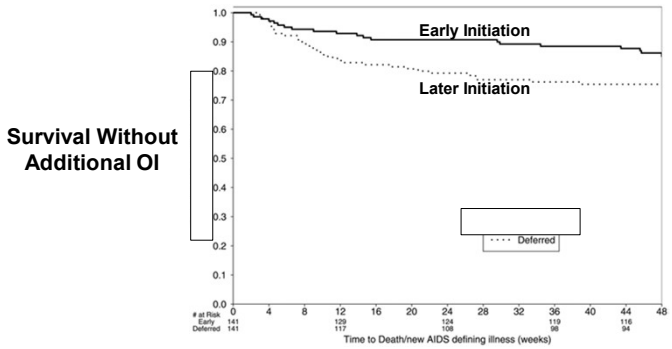
21

When to Start ART Following Opportunistic Infection

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

22

ART Initiation Following HIV Related Opportunistic Infections
Early Initiation (<2 weeks) Favors Survival



Zolopa PLoS One 2009;4:e5575

23

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

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

*For TB meningitis: potentially longer

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Primary and Secondary OI Prophylaxis

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

- **Primary Prophylaxis**
  - **PCP (CD4 <200, ~~oral candida, prior AIDS Defining~~)**
  - **Toxo (CD4 <100, old or new positive anti Toxo IgG)**
  - **Cocci (CD4<250, IgG or new positive cocci IgM**
  - **~~MAC (CD4 < 50)~~ ---NIH/CDC/IDSA guideline has eliminated this except patients whose VL can't be suppressed and have CD4 less than 50**
  - *
- **Secondary Prophylaxis /Chronic Suppression**
  - **PCP**
  - **Toxo**
  - **MAC**
  - **CMV**
  - **Cryptococcus**
  - **Histoplasma**
  - **Coccidio**

***Some experts would give Histo primary prophylaxis with itraconazole in high-risk situations if CD4<150/200 and would not use histo serology in decision (not reliable)**

25

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

Primary Prophylaxis	CD4 Count Due to ART
– PCP or Toxo	>200 x 3 months
– PCP	(>100 and VL<50)
Secondary Prophylaxis/Chronic Maintenance	
– PCP	>200 x 3 months
– Toxo	>200 x 6 months
– Crypt	>200 x 6 months
– MAC	>100 x 6 months + 12 m Rx
– CMV	>100 x 3-6 months*

26

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

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

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

27

Primary Coccidiomycosis Prophylaxis 2025 OI Guideline

Serologic Testing in Endemic Areas

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

Primary Prophylaxis

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

28

Recommended Immunization Schedule for Adults and Adolescents with HIV

Vaccine	All People with HIV	Where Varies by Age	Where Varies by CD4 Cell Count (cells/mm³)	
			<200	≥200
Hepatitis A	Two to three doses (varies by formulation)			
Hepatitis B	Two to four doses (varies by formulation and indication)			
Human papillomavirus (HPV)		Three doses for ages 18–26*		
Influenza	One dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	Two doses if born after 1956 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	Two doses, booster every 5 years			
Meningococcal B (MenB)	Two to three doses (varies by formulation)			
Mpox (MVA-BN, attenuated)	Two doses			
Mpox (ACAM2000, live replicating)	Contraindicated			
Pneumococcal conjugate (PCV15 or PCV20)	One dose			
Pneumococcal polysaccharide (PPSV23)	One dose (if conjugate vaccine was PCV-15)			
COVID-19	For current COVID-19 vaccination recommendations, please visit CDC.gov.		Recommendations differ with advanced or untreated HIV infection	
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years			
Varicella (VAR)			Contraindicated	Two doses
Zoster recombinant (RZV)		Two doses for ages 18 and older		

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

29

Recommended Immunization Schedule for Adults and Adolescents with HIV

This is All Oversimplified, But for the Exam

- **Avoid live vaccines at CD4 counts < 200 or Uncontrolled Viral Replication**
  - **MMR, Varicella, Yellow Fever, Oral typhoid, *Intranasal Influenza**
  - **But…Mpox Jynneos live vaccine is safe because it is non replicating**
- **Administer**
  - **HAV, HBV, Meningococcus ACWY, Pneumococcus, COVID**
    - **All higher incidence or more severe in HIV than non-HIV**
  - **RZV (Shingrix) age >18 years**
  - **Pneumococcus, when in doubt use PCV 20 or 21 –no follow up immuniz needed**
    - **(or PCV 15 plus 23 valent polysaccharide)**
- **Administer Mpox if possibly exposed or likely to be exposed**
- **Assess Post vaccine titers for HBV (and HAV if CD4<200)**

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

30

Who Should be Vaccinated for HBV

- **People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL)**
- **Current Recommendation**
  - **Two dose regimen**
    - **Conjugated vaccine: Heplisav-B® IM at 0 and 1 months**
  - **NIH/IDSA perspective re assessing post vaccine titers**
    - **1-2 months post vaccine and then some experts would test annually**
    - **Boost responders when annual level <10mIU/ml**

31

HBV Non-Responders

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

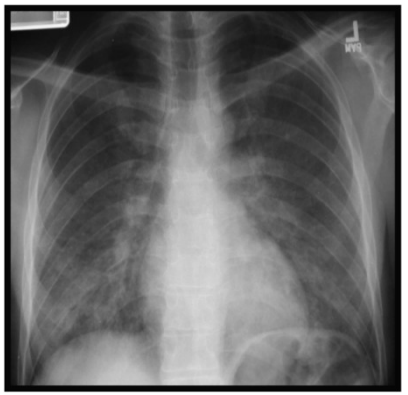
32

HBV Immunization for Persons with Isolated Anti HBc

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

33

HIV Associated Pulmonary Disease



34

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

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

35

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

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

36

Approach to Diagnosis and Therapy of Pneumonia in PWH

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

37

Etiology of HIV Associated Pulmonary Disorders

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

38

Pneumococcal Disease in Persons with HIV Infection

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

39

Internal Medicine Question

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

40

Strategies to Reduce Incidence of Pneumonia for Patients with HIV

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

41

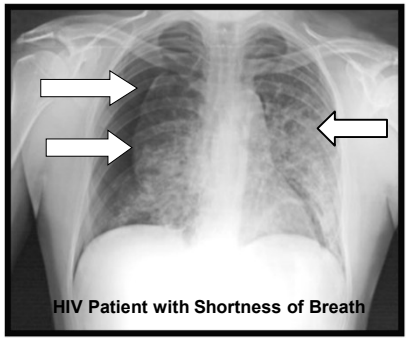
HIV and Covid

- No increased susceptibility
- Probably increased severity
  - May be primarily linked to other co-morbidities
- Drug interactions
  - Paxlovid and Remdesivir
    - No major interaction with Integrase inhibitors and Cobicistat

42

Question #4

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


HIV Patient with Shortness of Breath

43

Question #4

What is the most likely INFECTIOUS cause of this pneumothorax?

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

44

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

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

45

Host Susceptibility to PCP

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

46

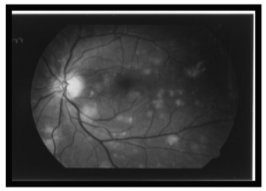
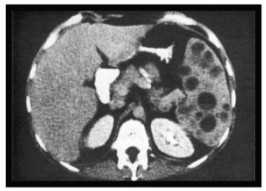
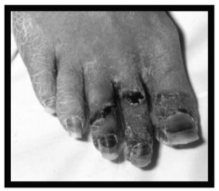
PCP is More Subacute in Persons With HIV Than Other Immunosuppressed Persons

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

Kovacs et al. Ann Intern Med 1984

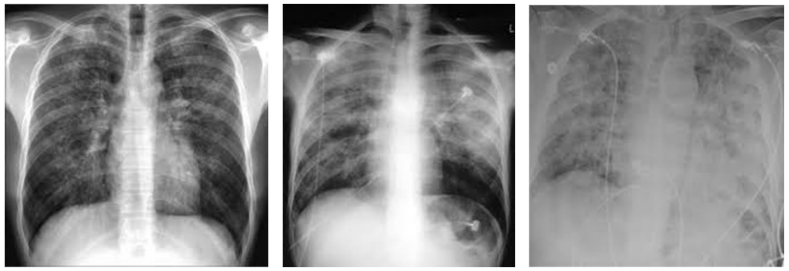
47

Uncommon Manifestations of PCP

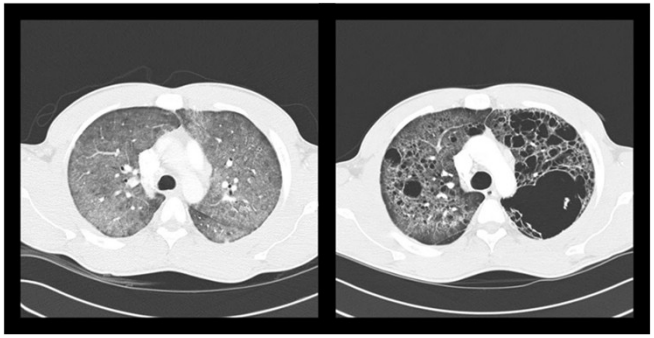
48

HIV Related PCP



49

Development of Pneumatocoeles



May 23 June 13

50

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

51

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- Other Patterns Recognized
  - Normal
  - Lobar infiltrates
  - Upper lobe infiltrates
  - Pneumothorax
  - Solitary nodules
  - Cavitating lesions
  - Infiltrates with effusions
  - Asymmetric or unilateral processes

52

Diagnosis of Pneumocystis Pneumonia

Specimen Acquisition		Organism Detection
Open lung biopsy	1957 ↓	Methenamine silver
Transbronchial biopsy		Immunofluorescence
Bronchoalveolar lavage		Giemsa / Diff Quik
Induced sputum	2025	PCR

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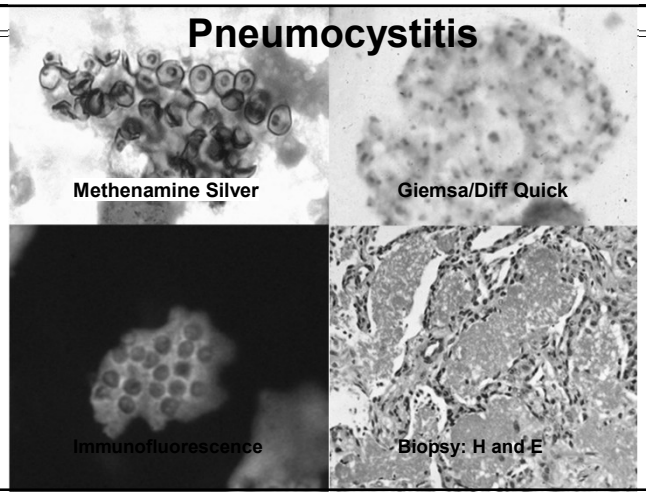
Pneumocystitis



54

PCR
Diagnosis of Pneumocystis
Bronchoalveolar Lavage or Sputum

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

55

PCR
Diagnosis of Pneumocystis
Bronchoalveolar Lavage or Sputum

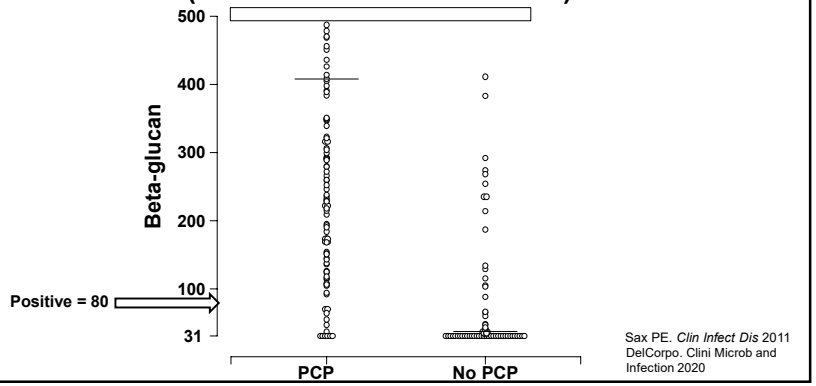
- High
  - Ins
- High
  - Po
  - Cy

Negative BAL PCR rules out PCP

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

56

Don't Use Beta Glucan Test for Diagnosis of PCP!! (Controversial---See Kotton)



Sax PE. *Clin Infect Dis* 2011
DelCorpo. Clini Microb and Infection 2020

57

Question #5

A 45-year-old woman with HIV (CD4 = 50 cells/uL, HIV viral load = 500,000 copies/uL) presents with fever, shortness of breath, room air P02 =80mm Hg) and diffuse bilateral infiltrates and is started on TMP-SMX.

The bronchoalveolar lavage is positive for pneumocystis by direct fluorescent antibody test.

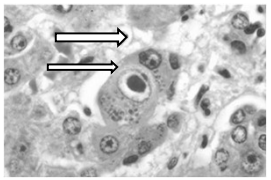
The microbiology lab also reports the BAL positive by PCR for CMV

What would be the best course of action in addition to considering antiretroviral therapy?

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

58

CMV and Lungs



Eosinophilic Intranuclear Inclusion and Basophilic Cytoplasmic Inclusions

CMV almost never causes pneumonia …In PWH

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

59

Question #6

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

Ten days later the patient returns with headache, exercise intolerance, shortness of breath, and you order a chest CT which is…normal

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

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

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

60

Two Pharmacologic Issues To Watch For

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

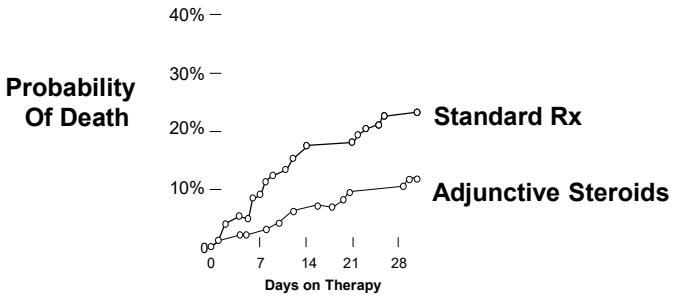
61

Therapy for HIV Related Pneumocystis Pneumonia

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

62

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



(Bozette, NEJM 5/90)

63

How to Manage Patients Who Are Failing TMP-SMX

- Deterioration common first 1-2 days (steroids)
- Average Time to Clinical Improvement
  - 4-8 Days
- Radiologic Improvement
  - Lags clinical improvement

64

Reasons to Deteriorate During Treatment for PCP

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

65

Reasons to Deteriorate During Treatment for PCP

- **Fluid ove**
  - Iatrogeni ine related)
- **Anemia**
- **Methemo**
  - Dapsone
- **Pneumot**
- **Unrecog**
- **Immune**

Patients Failing TMP-SMX Not Testable!

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

66

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

67

Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

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

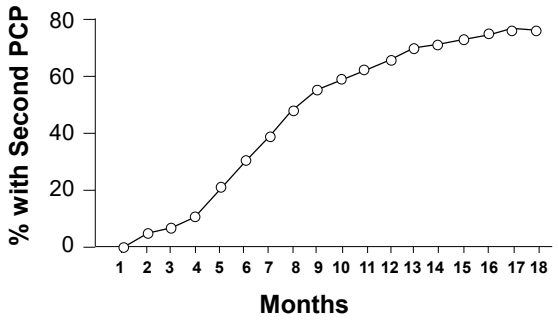
68

Toxicity and Other Considerations Regarding Antipneumocystis Therapy

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

69

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



Fischl/ACTG 002, 10/88

70

Indications for Primary and Secondary PCP Prophylaxis

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

71

Non-HIV---What Are Risk Factors and Timeline of Risk

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

72

Primary or Secondary Prophylaxis for Pneumocystis Pneumonia

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

73

Thank You!

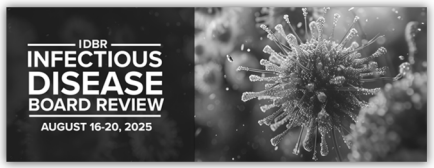
74

Tuesday, August 19, 2025

35

HIV Diagnosis

Frank Maldarelli, MD



HIV Diagnosis

Frank Maldarelli, MD
Bethesda, MD

7/22/2025

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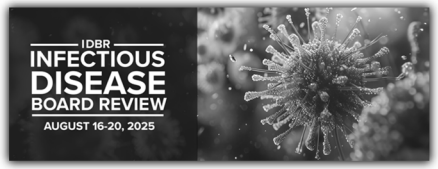


Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or "None"

2

Question #1

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

What is the most likely explanation for these results?

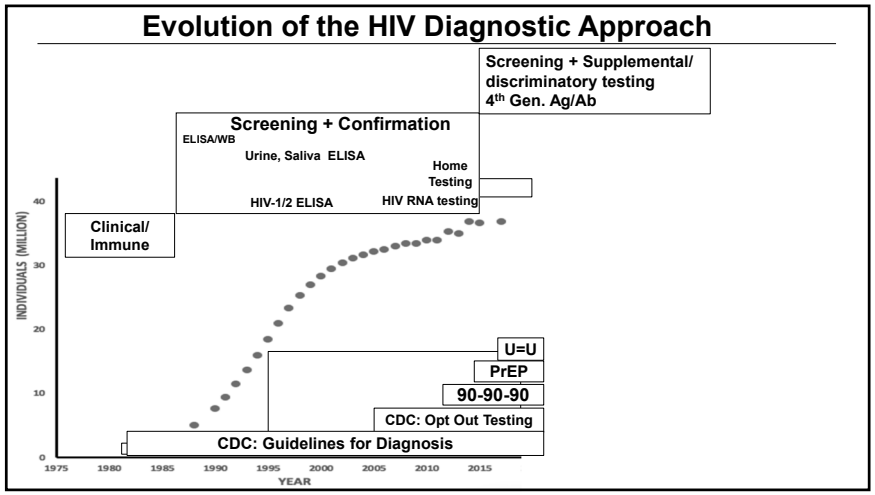
A. This person HIV-infected and is an elite controller
B. This person is HIV-infected but is in the window period for HIV infection
C. This person is infected with an HIV variant that is not detected by the supplemental test
D. This person is not HIV-infected

3

HIV Diagnosis: New Modalities and New Terminology Old Limitations Persist

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

4



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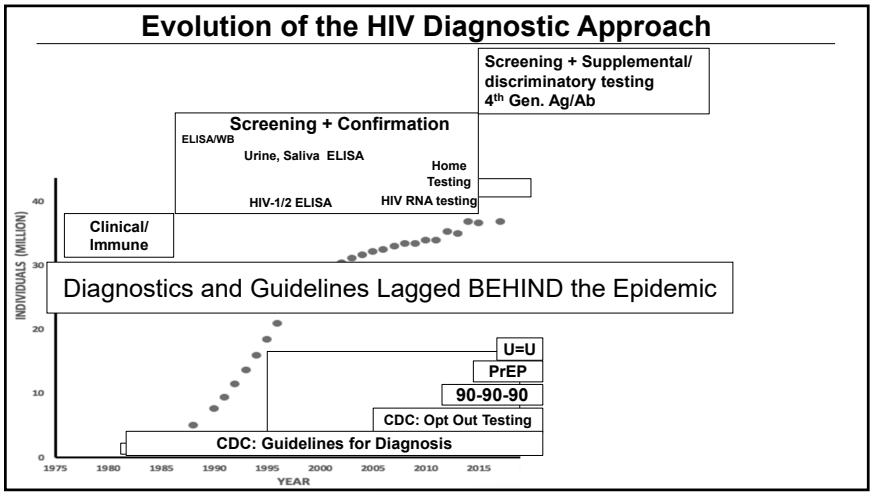

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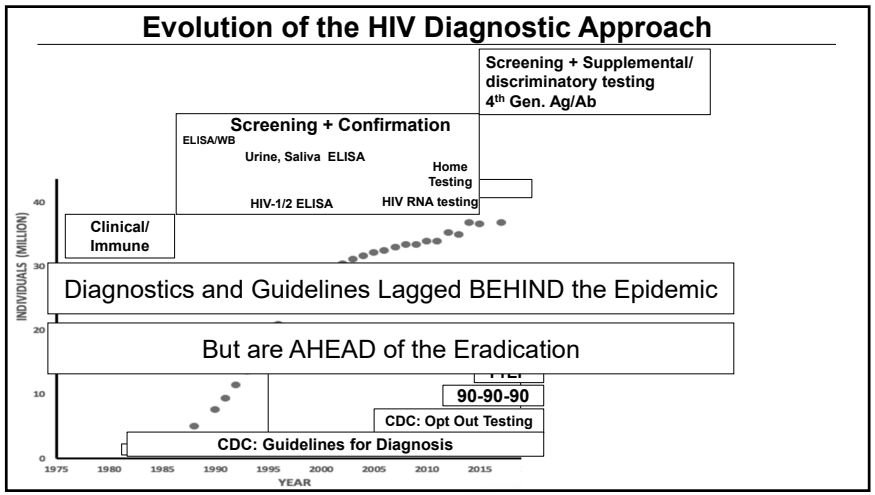

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Question #2

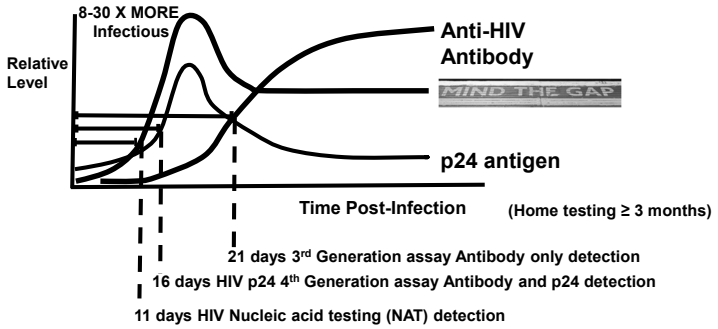
27-year-old female commercial sex worker working in Washington DC visits your clinic and requests PrEP. She shows you her home HIV test, which she took yesterday, and which is non-reactive. She has normal laboratory results and a negative pregnancy test.

Which of the following is most appropriate next step?

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

8

HIV Detection: There is Always a Window Period



CDC 2014

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Detecting HIV Infection TWO STEPS

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

10

Diagnosis of Early HIV Infection

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

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Evaluation for HIV Infection During PrEP

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

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Question #3

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

What is the most appropriate next step?

A. Obtain the HIV viral RNA test to find out how high the viral load is, and begin antiretroviral therapy immediately
B. Consider laboratory error, repeat the same 4th generation test
C. Perform supplemental testing with third generation discriminatory testing
D. Reassure the couple that the woman is not infected and the test is just a false positive

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HIV Serologic Testing Pregnancy

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

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Question #4

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

Which of the following is most likely?

A. The patient is in the window period of HIV-1 infection
B. The patient is chronically infected with HIV-1 and has a viral load too low to be detected because he is a long term non progressor
C. The patient is not infected with HIV-1 or -2, all tests are false positive
D. The patient is infected with non-B subtype of HIV-1

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HIV-1 Long Term Non-Progressors

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

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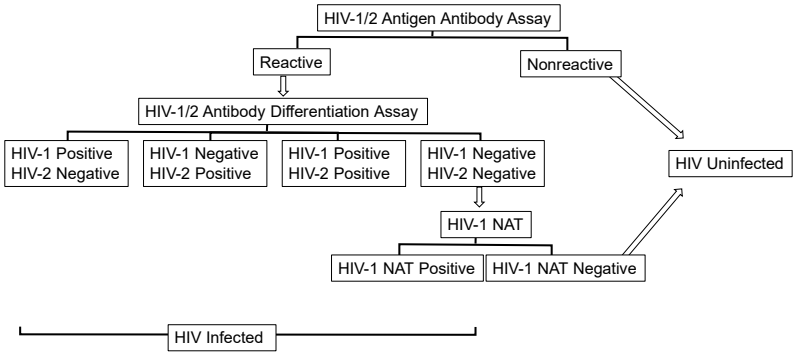
HIV Diagnostic Algorithm



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Question #5

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

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

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Question #5

Which of the following is most correct?

A. Tell him the Covid test was a false positive, he has HIV, and should start TDF+FTC+boosted darunavir
B. Tell him the HIV test is a false positive and continue PrEP
C. Tell him he may have HIV infection, send supplemental testing and continue PrEP
D. Tell him he may have HIV infection, send supplemental testing and switch to TDF+FTC+ Rilpivirine

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Question #6

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

What is the most likely explanation for these results?

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

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MANY HIV Screening False Positives

- **Infections**
  - COVID
  - African trypanosomiasis
  - Babesiosis
  - Schistosomiasis
  - Malaria
  - Dengue
  - Mycobacterial
  - Hepatitis A/C
- **Hematologic**
  - Polyclonal B cell responses
  - Heterophile antibodies
    - Workers in pork processing plant
  - B cell lymphoma
  - Autoimmunde hemolytic anemia
  - Angioblastic T cell lymphoma
  - Hodgkin lymphoma
- **Rheumatologic diseases**
  - Lupus
  - Sjorgen
  - Rheumatoid
- **Iatrogenic**
  - Vaccines
    - Rabies
    - Tdap
    - Hepatitis B
    - SARS-CoV-2
    - HIV vaccine trials
- Lentiviral therapy (e.g., CAR T)

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HIV Testing

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

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Pearls for Board Exam

HIV Testing is Comprehensive

- Non-B Subtypes are all detectable
- HIV-2 has an approved diagnosis
- Long term Non-Progressor
  - ELISA reactive / Supplemental Positive

Resources:

- https://www.cdc.gov/hiv/guidelines/testing.html
- Fmaldarelli3@gmail.com
- Reference slides follow

No test is perfect

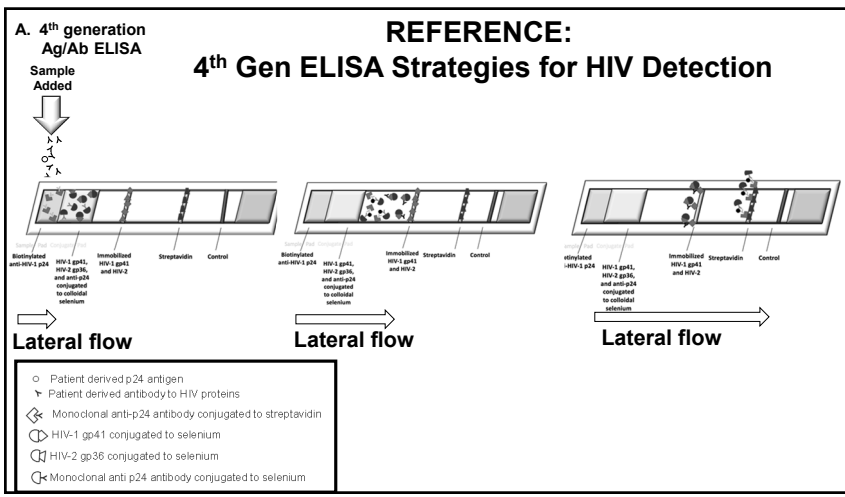
- 4th Gen less sensitive
  - Acute
  - PEP/PrEP
  - Early Antiretroviral therapy
- False Positives
  - Pregnancy
- Mind the gap
  - Long gap for Home testing

Board exam isn't perfect either

- **So don't overthink it**

23

REFERENCE:
4th Gen ELISA Strategies for HIV Detection



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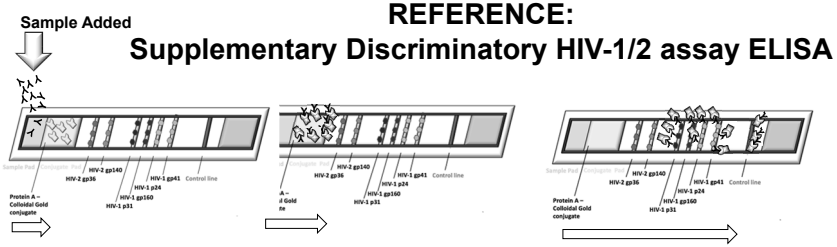
35 HIV Diagnosis
Speaker: Frank Maldarelli, MD

REFERENCE:
Supplementary Discriminatory HIV-1/2 assay ELISA



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

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Figure 7A

HIV Diagnostic Algorithm

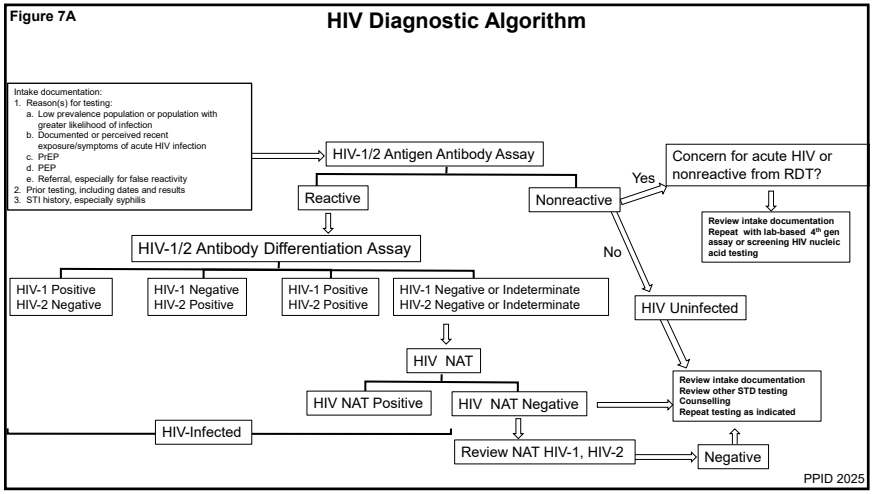

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Figure 7B

HIV Diagnostic Algorithm: PrEP Initiation

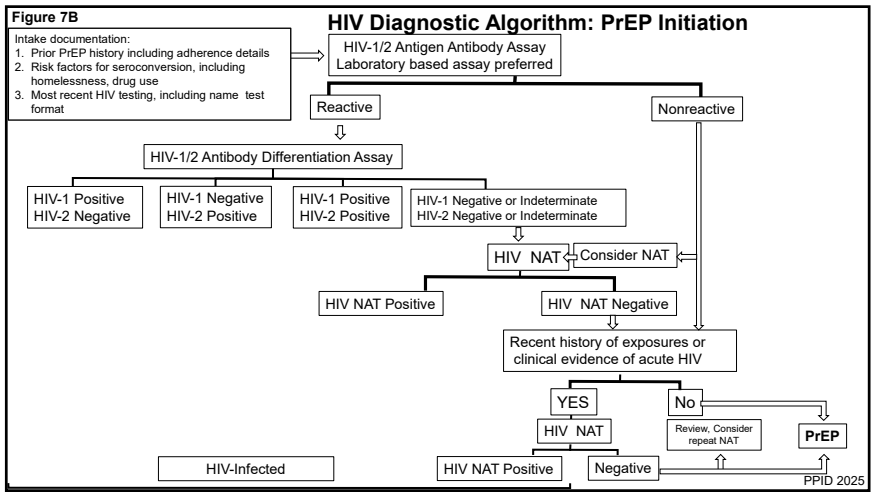

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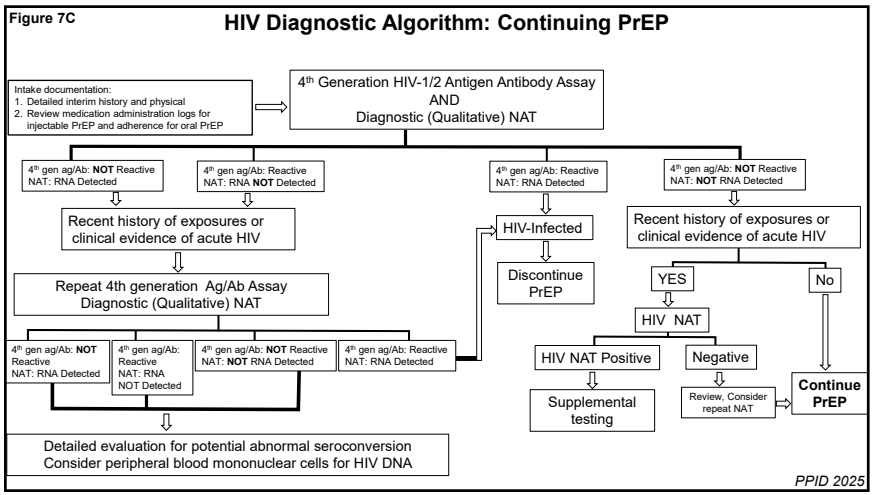
Figure 7C

HIV Diagnostic Algorithm: Continuing PrEP



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Tuesday, August 19, 2025

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Antiretroviral Therapy

Roy Gulick, MD

Antiretroviral Therapy (ART)

Roy M. Gulick, MD, MPH

Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

7/22/2025

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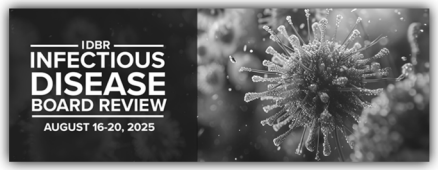

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

ID Boards – Medical Content: 15% HIV

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

3

ID Boards – Medical Content: 15% HIV

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

4

Antiretroviral Therapy (ART)

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

5

When To Start?

6

Question #1

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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

Do you recommend starting ART?

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

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When to Start? Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2024 www.clinicalinfo.hiv.gov	Recommended				
IAS-USA 2024 Gandhi JAMA 2025;333:609-628	Recommended				

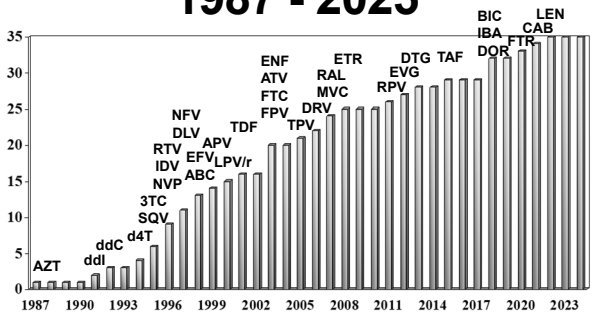
8

Goal of Antiretroviral Therapy

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

9

Antiretroviral Drug Approval: 1987 - 2025



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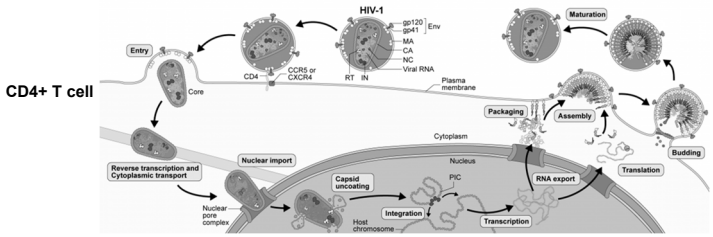
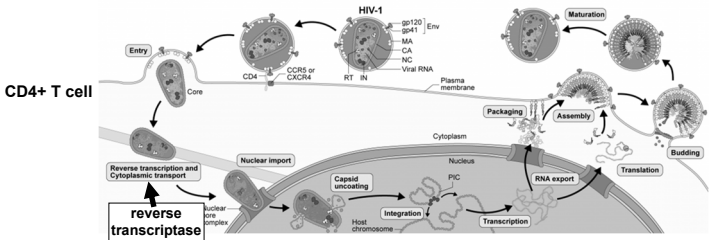
Life Cycle of HIV



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

11

Life Cycle of HIV



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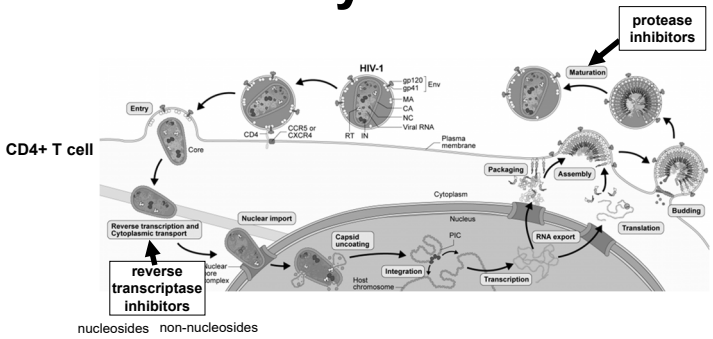
Life Cycle of HIV



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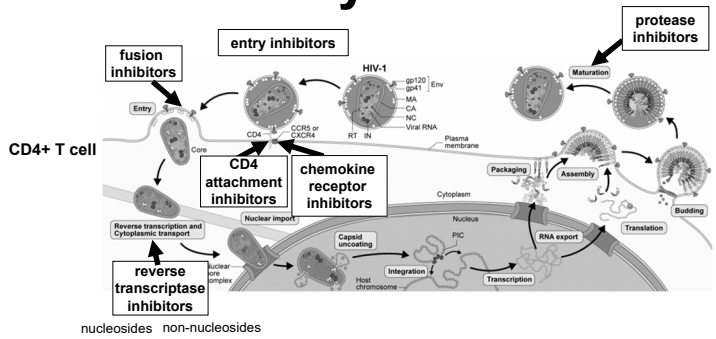
Life Cycle of HIV



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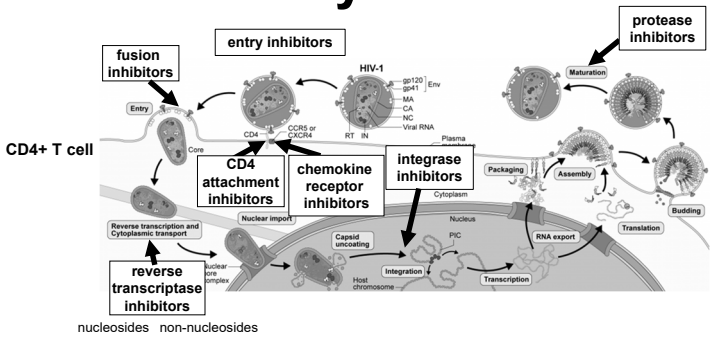
Life Cycle of HIV



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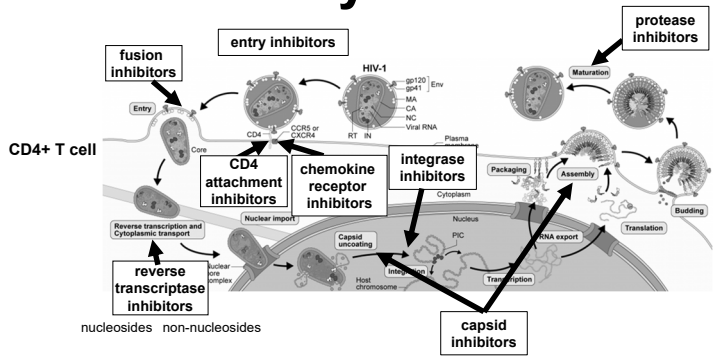
Life Cycle of HIV



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

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Approved ART: 2025*

Nucleoside/tide RTIs (NRTIs)
- Zidovudine (ZDV, AZT)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir (TAF, TDF)

NNRTIs
- Nevirapine (NVP)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)
- Doravirine (DOR)

Protease inhibitors (PIs)
- Ritonavir (RTV)
- Nelfinavir (NFV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Tipranavir (TPV)
- Darunavir (DRV)

Integrase inhibitors (IIs)
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)
- Bictegravir (BIC)
- Cabotegravir (CAB)

Entry inhibitors (EIs)
- Maraviroc (MVC, CCR5 antagonist)
- Ibalizumab (IBA, CD4 post-attachment inhibitor)
- Fostemsavir (FTR, CD4 attachment inhibitor)

Capsid inhibitors (CIs)
- Lenacapavir (LEN)

*ddI, ddC, d4T, DLV, APV, SQV, IDV, FPV, ENF (T-20) discontinued from U.S. market

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What To Start?

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Question #2

You have been monitoring a 36-year-old man with HIV, CD4 ~350, VL 636,000 who is now ready to start ART, and wants "a simple-to-take" regimen.

Which of these regimens do you recommend?

A. IM cabotegravir/rilpivirine
B. Dolutegravir/rilpivirine
C. Tenofovir alafenamide/emtricitabine/rilpivirine
D. Dolutegravir/lamivudine
E. Tenofovir alafenamide/emtricitabine + dolutegravir

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First ART Regimen: Individual Factors

- Antiretroviral activity (VL, CD4, clinical responses)
- Durability of responses
- Baseline drug resistance
- Tolerability
  - Acute side effects
  - Chronic side effects
- Convenience (number of pills, dosing interval, food/fasting requirements)
- Preserving future treatment options
- Stage of HIV disease, concomitant illnesses and medications (drug-drug interactions)
- Access and cost

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

- Integrase inhibitor-based
  - **Bictegravir**/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - **Dolutegravir** + tenofovir (TAF or TDF) + (FTC or lamivudine [3TC])
  - **Dolutegravir**/lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
- With a history of cabotegravir as PrEP: do integrase genotype
  - **Darunavir**/(cobicistat or ritonavir) + (TAF or TDF) + (FTC or 3TC)

U.S. DHHS Guidelines 9/12/24 clinicalinfo.hiv.gov

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Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - **Dolutegravir**/abacavir*/lamivudine
- Protease inhibitor-based (Boosted PI + 2 NRTI)
  - **Darunavir**/(cobicistat or ritonavir) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - **Darunavir**/(cobicistat or ritonavir) + abacavir*/lamivudine

*Test for HLA-B*5701, do not use if positive

U.S. DHHS Guidelines 9/12/24 www.clinicalinfo.hiv.gov

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Alternative Regimens (Certain Situations) (2)

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

U.S. DHHS Guidelines 9/12/24 www.clinicalinfo.hiv.gov

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Choice of NRTIs

Combination	DHHS GL	Dosing	Toxicities	Considerations
Tenofovir (TAF or TDF)/ **Emtricitabine** (FTC)	Recommended	1 tab qd	Renal, bone (with TDF); ↓ toxicity with TAF	1-pill, once-daily formulations available
Abacavir/ Lamivudine (ABC/3TC)	Alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; less effective with VL >100K; ↑MI
Zidovudine/ Lamivudine (ZDV/3TC)	No longer recommended	1 tab bid	GI, anemia, lipoatrophy	Toxicity

Based on DHHS Guidelines 9/12/24

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Choice of NRTIs

Drug	DHHS GL	Dose	Toxicities	Considerations
Doravirine (DOR)	Alternative	qd	↓ CNS toxicity than EFV; ↓ lipids	TDF/FTC/DOR (1 pill, once-daily)
Rilpivirine (RPV)	Alternative	qd	Not well absorbed with PPI	(TAF or TDF)/FTC/RPV (1 pill, once-daily with a meal); NOT for HIV RNA >100K or CD4 <200
Efavirenz (EFV)	No longer recommended	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
Nevirapine (NVP)	No longer recommended	qd or bid	Hepatotoxicity, hypersensitivity	Toxicity

Based on DHHS Guidelines 9/12/24

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Choice of PIs

Drug	DHHS GL	Dose	Toxicities	Considerations
Darunavir /(Cobicistat or Ritonavir) (DRV/C or R)	Alternative; preferred if integrase inhibitor exposure	qd (if no prior PI resistance) or bid	Skin rash (rare);	Active against PI-resistant viral strains
Atazanavir /(Cobicistat or Ritonavir) (ATV/C or R)	No longer recommended	qd	↑ indirect bilirubin, GI	Avoid PPI; kidney stones (uncommon); low Barrier to resistance
Lopinavir/ Ritonavir (LPV/R)	No longer recommended	bid or qd	diarrhea, ↑lipids	Co-formulated

Based on DHHS Guidelines 9/12/24

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Choice of Integrase Inhibitors

Drug	DHHS GL	Dosing	Toxicities	Considerations
Bictegravir (BIC)	Recommended with TAF/FTC	1 coform-ulated pill	Few, ↑creat, wt gain	TAF/FTC/BIC (1 pill, qd); binds divalent cations; ↑ barrier to resistance
Dolutegravir (DTG)	Recommended with (TAF or TDF)/(FTC or 3TC); alternative with ABC/3TC	50 mg qd (bid with II resistance)	Few, ↑creat, CNS, wt gain	ABC/3TC/DTG (1 pill, qd); binds divalent cations; ↑ barrier to resistance
Elvitegravir (EVG)	No longer recommended	1 coform-ulated pill	Mild GI	Drug interactions with cobicistat
Raltegravir (RAL)	No longer recommended	400 mg bid	Few	Twice-daily dosing; no co-formulations

Based on DHHS Guidelines 9/12/24

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Selected Drug Interactions (1)

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

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Selected Drug Interactions (2)

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

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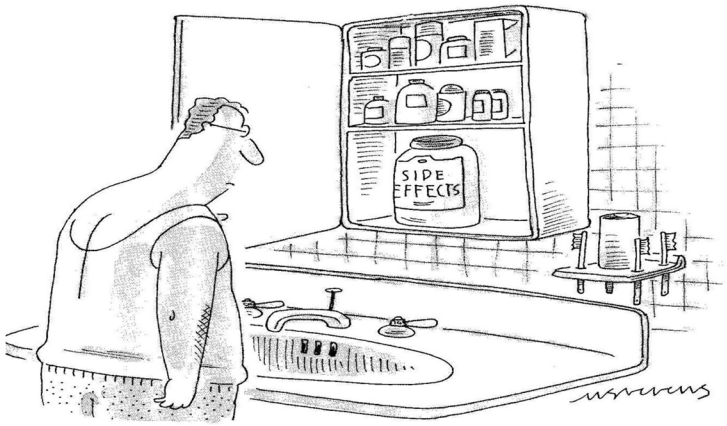
ART: What NOT to use as Initial therapy

- Monotherapy
- Nucleosides (NRTI)
  - 3 or 4 all-NRTI combination regimens
  - Older drugs (e.g. zidovudine, didanosine)
- Non-nucleosides (NNRTI)
  - Older drugs (e.g., efavirenz, nevirapine)
  - Etravirine
- Protease Inhibitors (PI)
  - Older drugs (atazanavir, lopinavir, nelfinavir, ritonavir [except as a booster], tipranavir)
- Integrase inhibitors (INSTI)
  - Elvitegravir or raltegravir
- Entry inhibitors (EI)
- Some 2-drug regimens
  - IM CAB/RPV or DTG/RPV

Based on DHHS Guidelines 9/12/24

30



31

ART: Side Effects (1)

- **Life threatening**
  - Hepatitis (NNRTIs, PIs)
  - Hypersensitivity reaction (HSR) (abacavir, nevirapine, etravirine)
    - Abacavir HSR greatly reduced by HLA-B*5701 screening
    - Stop nevirapine or etravirine for rash with constitutional symptoms
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - Teratogenicity
    - Efavirenz = pregnancy category D
    - Dolutegravir during conception/very early pregnancy → neural tube defects – RARE, not significantly ↑ vs. other ART

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ART: Side Effects (2)

- **Acute/early**
  - Gastrointestinal (zidovudine, TDF, PIs, ?all ART)
  - Anemia, neutropenia (zidovudine)
  - Bone mineral density ↓ (TDF)
  - Central nervous system (efavirenz, integrase inhibitors[?])
  - Fatigue (zidovudine)
  - Indirect hyperbilirubinemia (atazanavir)
  - Rash (NNRTIs)

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ART: Side Effects (3)

- **Chronic/longer term**
  - Cardiovascular (abacavir, PIs except atazanavir)
  - Kidney stones (atazanavir)
  - Metabolic – glucose, lactate, lipids (older PIs)
  - Morphologic:
    - Fat loss – lipoatrophy (stavudine, zidovudine)
    - Fat gain – lipohypertrophy (older PIs)
  - Proximal renal tubular dysfunction (TDF)
  - Weight gain (?) (TAF, bictegravir, dolutegravir)

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When to Change?

35

ART Change

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

Based on DHHS Guidelines 9/12/24

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Why Does Treatment Fail Patients?

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

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Question #3

28-year-old man with HIV on TDF/emtricitabine + atazanavir/ritonavir for 2 years with HIV RNA <50 cps/ml and CD4 200s→300s presents for routine follow-up; labs reveal HIV RNA 68 cps/ml and CD4 352.

What do you recommend?

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

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When to Change Therapy?

Virologic failure

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

Immunologic failure

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

Based on DHHS Guidelines 9/12/24

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What To Change To?

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What to Change To? U.S. DHHS Guidelines

- Review goal of therapy:
  - Maximal virologic suppression (HIV RNA below detection)
- Review ART history
- Assess adherence, tolerability, and PK
- Perform resistance testing while on drugs (or within 4 weeks of d/c of ART)
- Identify susceptible drugs/drug classes (e.g. fostemsavir, lenacapavir)
- Do not add a single active drug to a failing regimen
- Goal:
  - Design a regimen with 2 fully active drugs (one with a high barrier to resistance: boosted darunavir, bictegravir, dolutegravir), or if no high-barrier drug available, 3 fully active drugs

DHHS Guidelines 9/12/24

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Treatment = Prevention

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Treatment = Prevention

- Pregnant women with HIV *Fowler NEJM 2016;375:1726*
  - 3-drug ART ↓ transmission risk to child to 0.5%
- Men and women with HIV *Cohen NEJM 2016;375:830*
  - Suppressive ART ↓ transmission to sexual partners by 93%
- HIV- post-exposure prophylaxis (PEP) *Tanner CDC Guidelines MMWR 2025;74:1*
  - 3-drug integrase inhibitor-based ART recommended for 4 weeks (e.g. TDF/FTC + DTG)
- At-risk men and women without HIV
  Molina NEJM 2015, McCormack Lancet 2016, Landovitz NEJM 2021, Delany-Moretlwe Lancet 2022; Choopanya Lancet 2013
  - PrEP ↓ HIV acquisition by sex >75-85% (TDF/FTC ♂♀; TAF/FTC ♂ only; IM CAB ♂♀)
  - PrEP ↓ HIV acquisition by injection drug use ~50% (TDF/FTC)

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Cure

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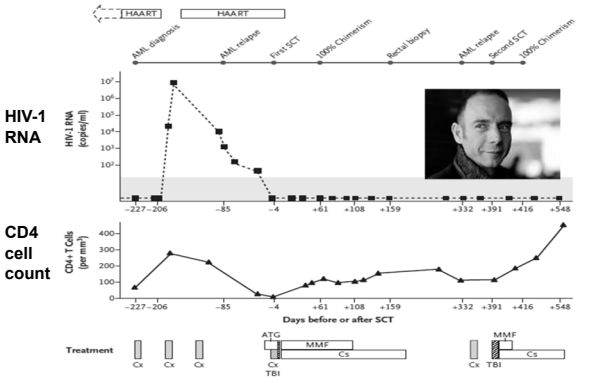
HIV Cure (N=1) 9!



Hutter NEJM 2009;360:692

Cure #2 *first Latino
London
Gupta, Nature 2019;568:244-248
Cure #3 *first woman
NYC
Hsu, Cell 2023;186:1115-1126
Cure #4
Dusseldorf
Jensen, Nat Med 2023;29:583-587
Cure #5
City of Hope
Dickter, NEJM 2024;390:669-671
Cure #6 *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544-3554
Cure #7 *first Δ32 hetero donor
Berlin
Gaebler, et al IAS 2024
Cure #8 *HIV rebound
Chicago
Rubinstein CROI 2025 #531
Cure #9
Oslo
Troseid CROI 2025 #532

45

ART: Conclusions

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

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Acknowledgements

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

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Tuesday, August 19, 2025

37

HIV Drug Resistance

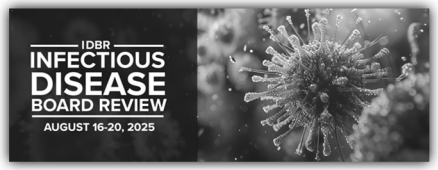
Michael Saag, MD

HIV Drug Resistance

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

7/22/2025

1



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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How Does Resistance Happen?

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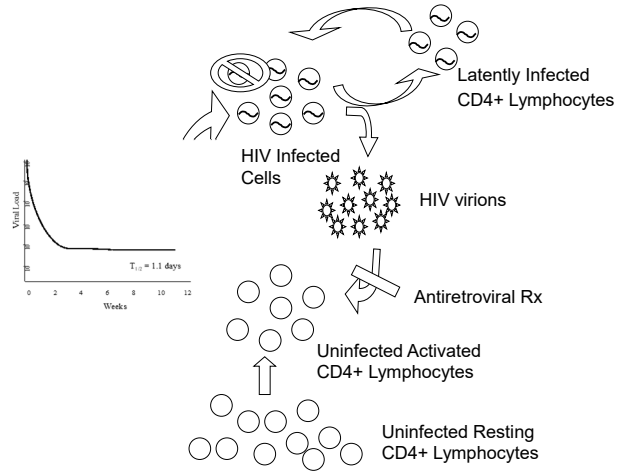

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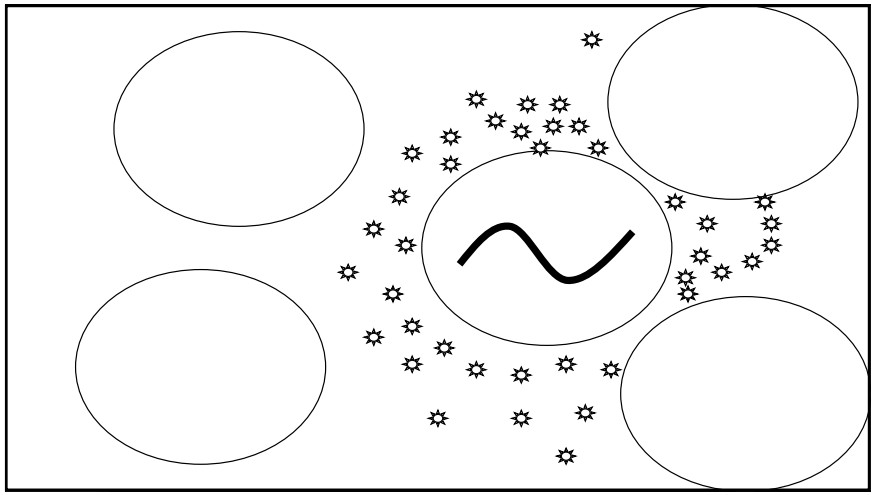

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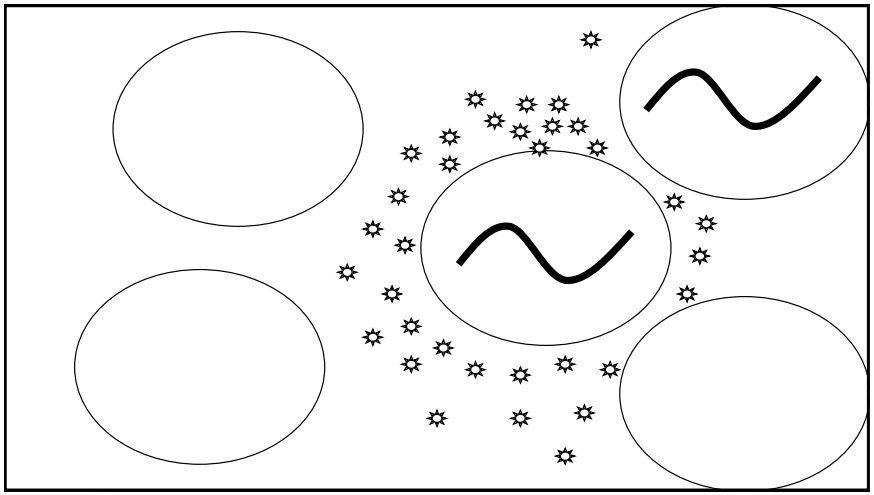

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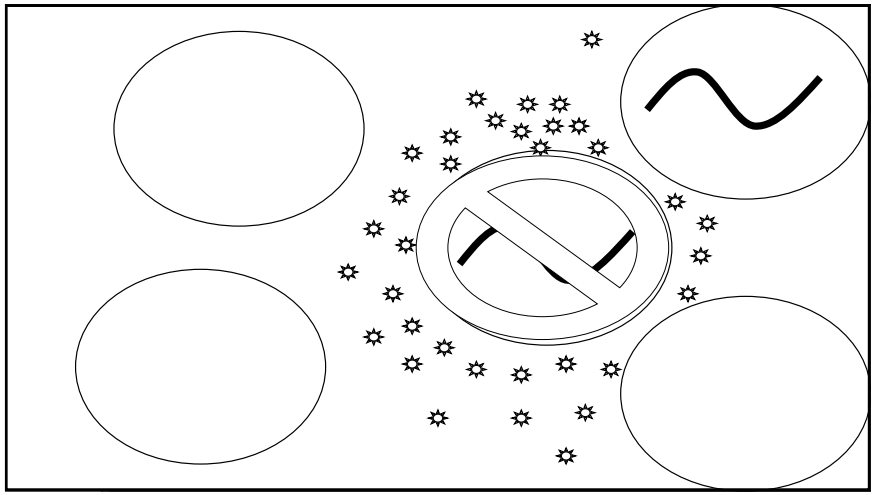

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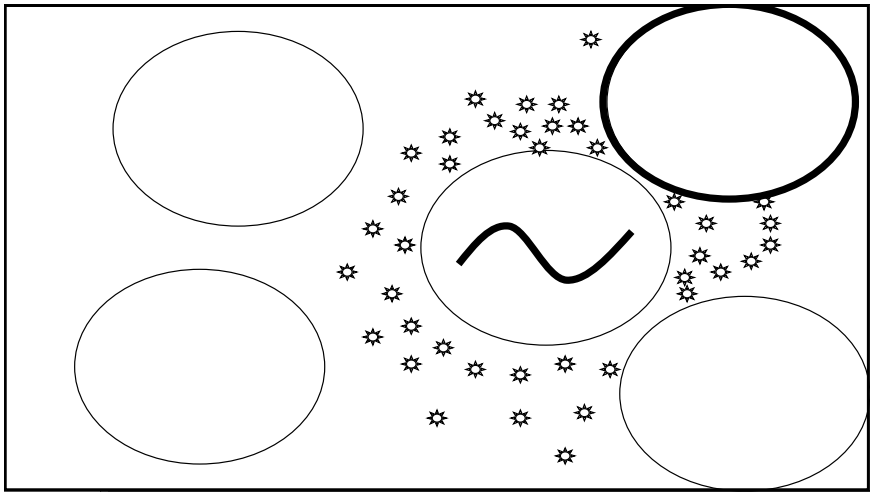

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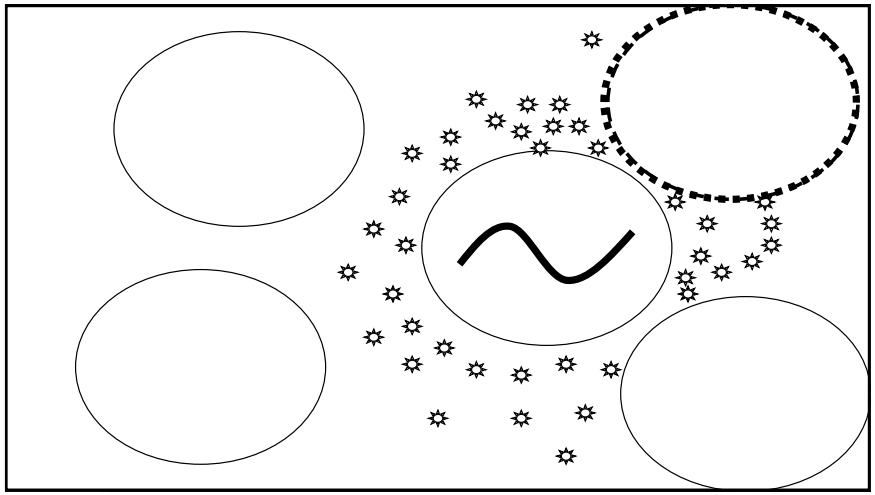
37 HIV Drug Resistance

Speaker: Michael Saag, MD



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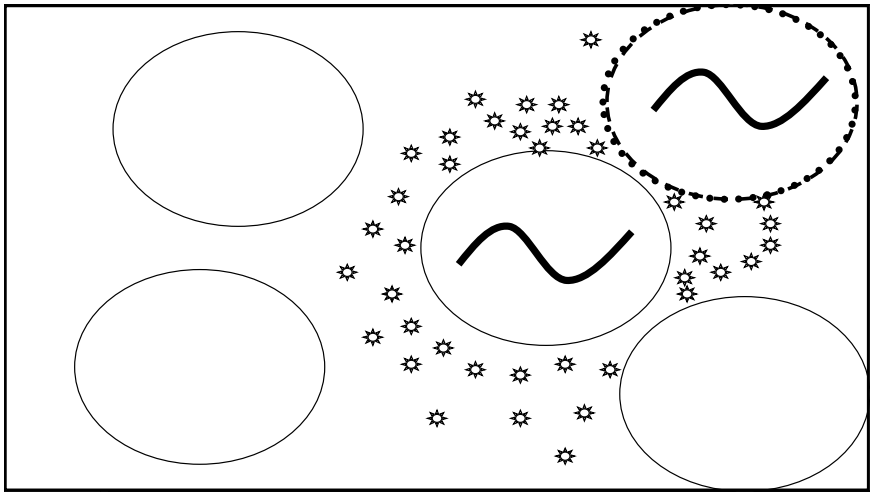

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Resistance Testing

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

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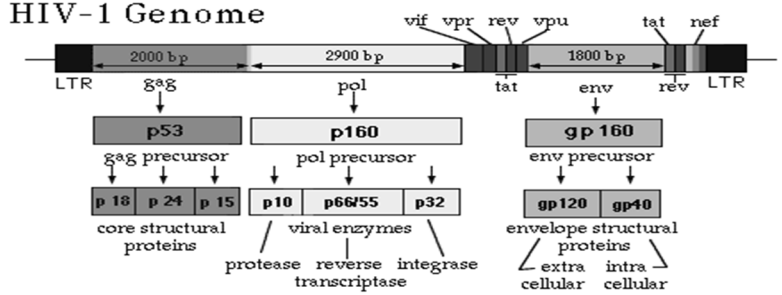
HIV Drug Resistance Testing

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

12

HIV-1 Genome



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Mutation Nomenclature

Codon (position)

PR = 1-99 amino acids

RT = 1-560 amino acids

↓

M184V

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Mutation Nomenclature

Codon (position)

PR = 1-99 amino acids

RT = 1-560 amino acids

↓

M184V

Wild-type amino acid (consensus)

Mutant amino acid

Table 1. Amino acids and their abbreviations.

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

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Question #1

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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

He wants to start ARV therapy

A baseline genotype is ordered that shows an M184V mutation.

Which of the following drugs will have reduced susceptibility with this mutation?

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

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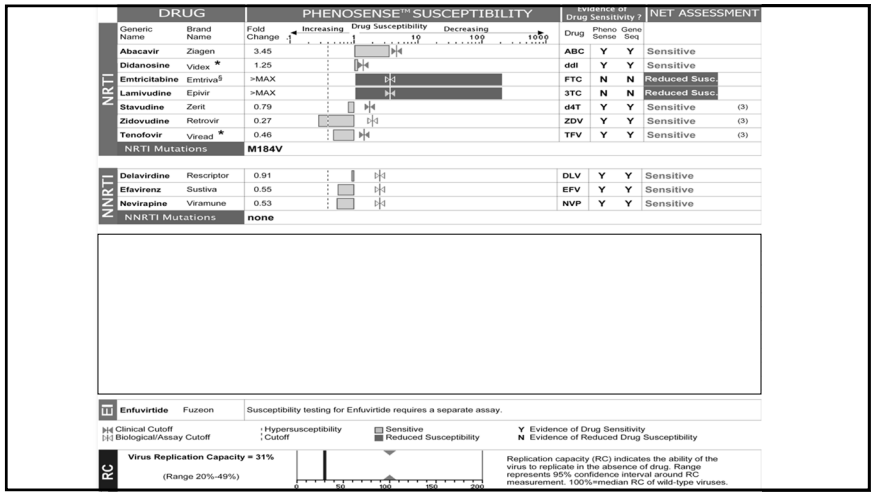

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Question #2

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

18

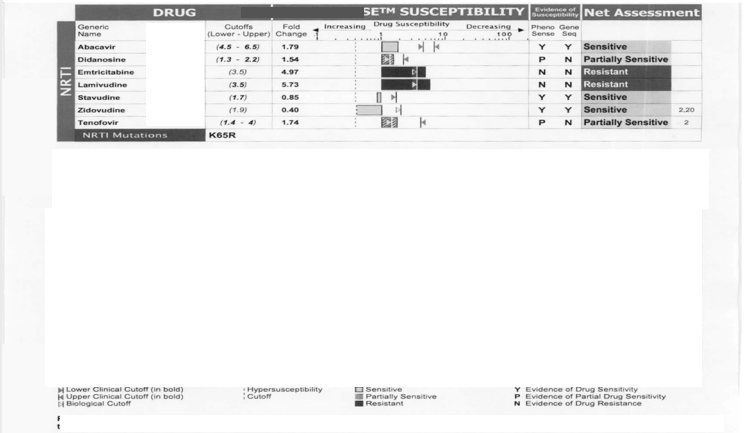
Question #2

The genotype shows an M184V and K65R mutations.

Which nRTI drugs would you include?

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

19



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Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

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

21

Question #3

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

22

Question #3

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

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

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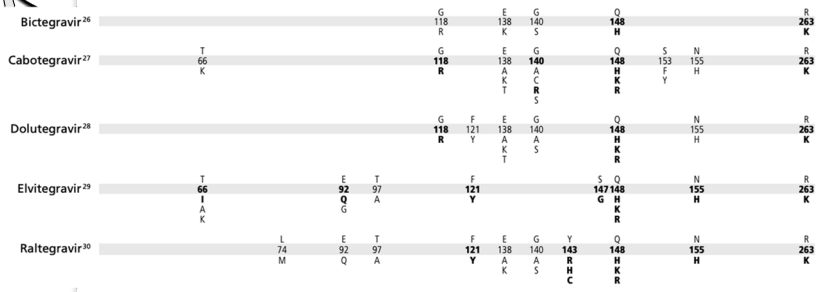
InSTI Resistance Mutations



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Lenacapavir Resistance Mutations

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

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

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Question #4

- 34-year-old MSM receiving CAB IM q 2 months for pre-exposure prophylaxis for last 6 months; Hasn't missed a dose
- Asymptomatic
- HIV Ag/Ab test negative
- Routine screening: HIV RNA 6.1 c/ml

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Question #4

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

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

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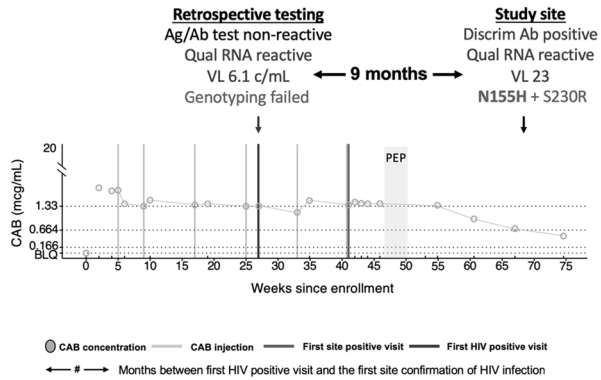
Case Study: Confirmation of Infection



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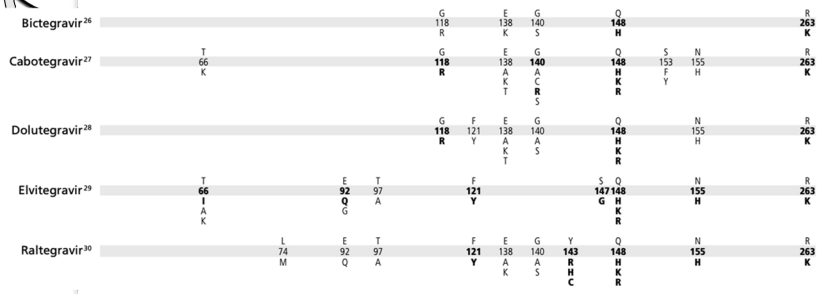
InSTI Resistance Mutations



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Question #5

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

30

Question #5

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

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

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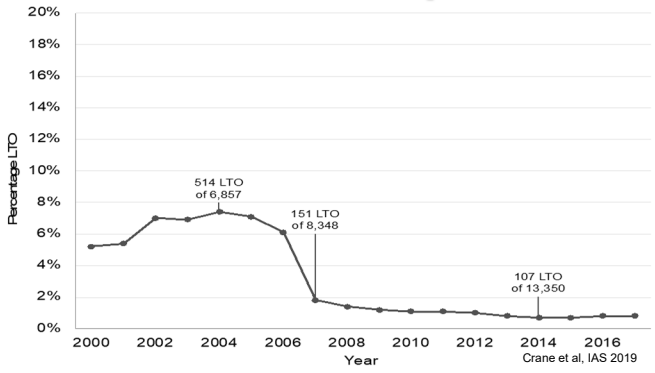
Prevalence of Patients with Limited Treatment Options



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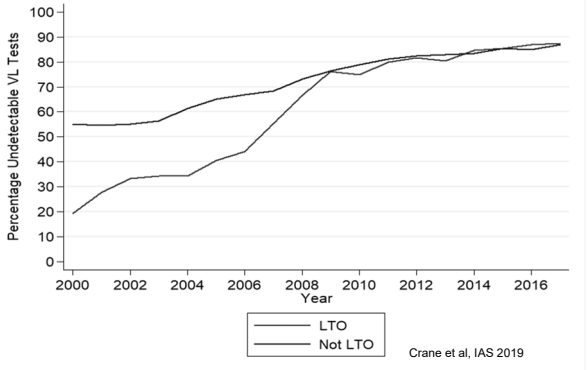
Virologic Success in Those with or without LTO



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Common Mutations To Memorize

• **M184V/I**	3TC and FTC
• **K65R**	Tenofovir
• **K103N**	EFV retains susceptibility to etravirine
• **Y181C**	Many NNRTIs
• E138K, K101E	RPV and other NNRTI
• I50L	ATV
• **N155H, Q148H/R/K**	RAL and EVG
• **Y143C**	RAL
• **R263K**	DTG

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Summary

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

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- **Contact me: msaag@uabmc.edu**

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Tuesday, August 19, 2025

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Antiretroviral Therapy for Special Populations

Roy Gulick, MD

Antiretroviral Therapy (ART) for Special Populations

Roy M. Gulick, MD, MPH

Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

7/22/2025

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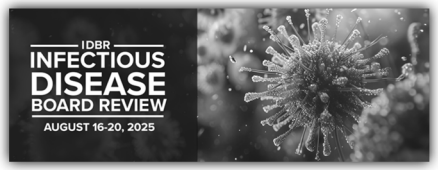

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Special Populations

- Acute/recent HIV infection
- Acute opportunistic infection
- Tuberculosis
- HIV-HBV co-infection
- HIV-HCV co-infection
- Pregnancy
- Post-HIV exposure (PEP)
  - Occupational (OPEP)
  - Non-occupational (NPEP)
  - Pre-HIV exposure (PREP)

3

Question #1

PREVIEW QUESTION

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

Which statement is correct?

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

4

Acute or Recent HIV

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

DHHS Guidelines 9/12/24

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Question #2

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

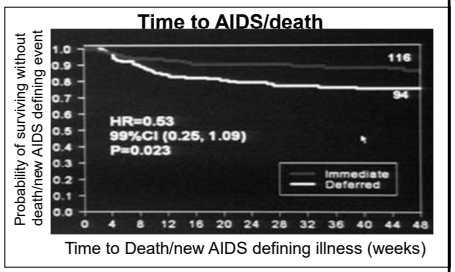
When should she start ART?

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

6

ACTG 5164: Immediate vs Delayed ART with an Acute OI

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



Zolopa PLoS One 2009;4:e5575

7

HIV-TB Co-infection

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

DHHS Guidelines 9/12/24

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Question #3

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

Which of the following ART regimens do you recommend?

A. TDF/emtricitabine/efavirenz
B. TDF/emtricitabine + atazanavir (unboosted)
C. TAF/emtricitabine + darunavir (boosted with cobicistat or ritonavir)
D. TAF/emtricitabine/bictegravir

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HIV-TB Co-infection (2)

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

DHHS Guidelines 9/12/24

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Question #4

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

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

Of the following, which ART regimen would you recommend?

A. Abacavir/lamivudine/dolutegravir
B. Cabotegravir + rilpivirine IM
C. Dolutegravir/lamivudine
D. Tenofovir (TAF or TDF)/emtricitabine + darunavir (boosted)

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HIV-HBV Co-infection

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

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HIV-HCV Co-infection

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

DHHS Guidelines 9/12/24

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Question #5

PREVIEW QUESTION

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

What do you recommend regarding ART?

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

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Antiretrovirals in Pregnancy

- ART recommended for <u>all</u> pregnant people, as early as possible, regardless of CD4 or VL level (rx and prevention of MTCT: mother to child transmission)
  - Perform drug-resistance testing if VL >500-1000 cps/ml
  - Start (or continue if safe/tolerated) <u>standard 3-drug ART</u> as early as possible (while awaiting drug resistance testing):
    - 2-drug regimens can be continued, if virologically suppressed
    - Modify regimen when drug resistance testing results available
  - ART does <u>NOT</u> increase the risk of birth defects
- Near delivery, if HIV RNA >1000 (or unknown), use intravenous zidovudine, and recommend Cesarean section at 38 weeks

DHHS Perinatal Guidelines 12/19/24 <www.clinicalinfo.hiv.gov>

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ART in Pregnancy: NRTI

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

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ART in Pregnancy: NNRTI

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

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ART in Pregnancy: PI

- Preferred:
  - Darunavir/ritonavir (when previously on cabotegravir PrEP; need to use bid)
- Alternative:
  - Atzanavir/ritonavir
  - Darunavir/ritonavir (need to use bid)
- Not recommended:
  - Cobicistat (↓ drug concentrations, limited experience)
  - Lopinavir/ritonavir (side effects, need to use bid; could continue if already taking; may need to ↑ dose)

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ART in Pregnancy: INSTI

- Preferred:
  - Dolutegravir (neural tube defects not significantly ↑ vs. other ART)
- Alternative:
  - Bictegravir
  - Raltegravir (need to use bid)
- Not recommended:
  - Elvitegravir/cobicistat (↓ drug concentrations)
  - IM cabotegravir + rilpivirine

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ART in Pregnancy: Other

- **Not recommended:**
  - 2-drug regimens (e.g. dolutegravir/lamivudine, dolutegravir/rilpivirine, cabotegravir/rilpivirine IM)
  - Cobicistat as a booster (for EVG or PIs)
- **Only recommended for treatment-experienced:**
  - Etravirine, fostemsavir, ibalizumab, lenacapavir, maraviroc

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Question #6

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

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

A. Tenofovir (TDF or TAF)/emtricitabine
B. Tenofovir (TDF or TAF)/emtricitabine + non-nucleoside RT inhibitor (NNRTI)
C. Tenofovir (TDF or TAF)/emtricitabine + integrase inhibitor
D. Tenofovir (TDF or TAG)/emtricitabine + protease inhibitor

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Antiretrovirals for PEP (1)

Post-exposure prophylaxis (PEP) for **occupational** exposure:

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

PHS Guidelines updated 5/23/18

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Antiretrovirals for PEP (2)

PEP for **non-occupational** exposure:

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

- Testing: Do rapid HIV (Ag)/Ab test or if results not available, start PEP
- Prior to PEP: BUN/creatinine, LFTs, STI testing (CT, GC, syphilis), HBV/HCV testing, pregnancy testing
- Preferred Treatment: 4 weeks of
  - **TAF/FTC/bictegravir**
  - **Tenofovir (TAF or TDF)/(FTC or 3TC) + dolutegravir**

Tanner CDC Guidelines MMWR 2025;74:1-56

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Question #7

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

Which of these PrEP regimens do you recommend?

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

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CDC Guidance for PrEP:

- Inform all sexually active adults and adolescents about PrEP
- Before starting:
  - Exclude acute and chronic HIV infection (by HIV testing and symptoms)
  - Assess baseline CrCl, screen for STIs and HBV infection
- Prescribe PrEP for people with ongoing risk from sex or injecting drugs:
  - Tenofovir (TDF)/FTC for ♂ and ♀ (daily; some guidelines recommend "on-demand")
  - Tenofovir (TAF)/emtricitabine for ♂ ONLY (daily)
  - IM cabotegravir for ♂ and ♀ (every 2 months)
  - Provide risk reduction, adherence counseling, condoms
- On PrEP:
  - HIV testing every 3-4 months, monitor CrCl every 6 (age >50 or CrCl <90) or 12 months
  - Risk reduction, condoms, STI assessments/treatment
  - Evaluate the need to continue PrEP

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

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Conclusions

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

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

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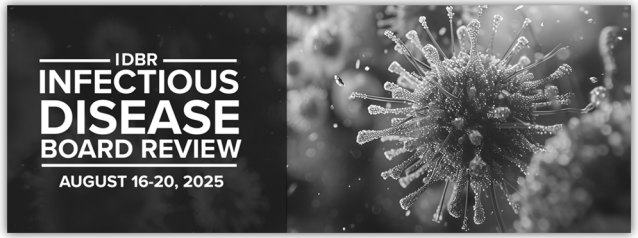
Tuesday, August 19, 2025

BR4

Board Review Day 4

Drs. Gulick (Moderator), Bloch, Gandhi, Maldarelli, Masur, Saag, and Tunkel



Board Review: Day 4

Moderator: Roy Gulick, MD

Faculty: Drs. Bloch, Gandhi, Maldarelli, Masur, Saag, and Tunkel

7/22/2025

1

BOARD REVIEW DAY 4

#46 **A 22-year-old man asks about HIV pre-exposure prophylaxis (PrEP) options. His friend takes "on-demand" PrEP and he asks your opinion.**

What do you respond?

A. On-demand PrEP cannot be recommended because it is not FDA-approved

B. On-demand is not recommended in current guidelines

C. On-demand PrEP has only been studied with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)

D. On-demand PrEP has not been studied in men-who-have-sex-with-men (MSM)

1 of 2

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BOARD REVIEW DAY 4

#47 **A 16-yr old male high school student from suburban Alexandria, Virginia presented with episodes during the past three months when he felt like his heart was "bursting from his chest" when he was doing push-ups in gym class.**

This went away promptly when he stopped exercising. He said it didn't feel like skipped beats and was not associated with chest pain or dyspnea.

He grew up in Iran, but his family has moved the USA four years previously. On exam, he was afebrile and appeared healthy.

A grade 3 systolic and diastolic murmur was heard at the left sternal border. Echocardiogram found mitral stenosis and regurgitation, with a thickened mitral valve without vegetations and an enlarged left atrium.

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BOARD REVIEW DAY 4

#47 **EKG showed first degree heart block with a PR interval of 300 msec and no extrasystoles.**

Routine chemistries and CBC were normal but CRP and ESR were elevated.

Which of these tests would be the most helpful in diagnosis?

A. Anticardiolipin IgG

B. Anti dsDNA

C. Anti Coxiella burnetii phase 2 IgG

D. Anti streptococcal DNase B

E. PCR on blood for Tropheryma whipplei

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BOARD REVIEW DAY 4

#48 **A 35-year-old woman presents to her primary care clinic with 6 weeks of cough, shortness of breath, and new skin lesions. She has no fever or weight loss. She is found to be HIV positive (CD4 count 150 cells/mm3 and HIV viral load 500,000 copies/mL).**

She has lived in Delaware all of her life, with no long-distance travel. She has no unusual pets or exposures although she does admit to commercial sex work over the past two decades.

On physical examination she has multiple purple-red skin lesions on her face, trunk and extremities.

Her PaO2 on room air is 95% and her routine blood count and chemistries are normal.

1 of 4

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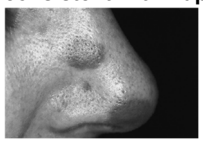
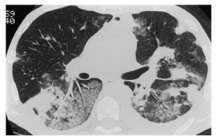
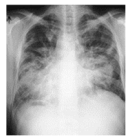
BOARD REVIEW DAY 4

#48 **Her chest x-ray is strikingly abnormal, as is her chest CT scan which is read as showing reticular nodules, consolidation, and effusions consistent with Kaposi sarcoma.**

https://phil.cdc.gov/Details.aspx?pid=6436

Serologic studies for cryptococcus and histoplasma are negative, and she is IGRA negative.

Induced sputum studies are negative for PCP (PCR), routine culture, and mycobacterial and fungal cultures at 7 days.

2 of 4

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BOARD REVIEW DAY 4

#48 **How would you evaluate the cause of the pulmonary and endobronchial lesions before starting treatment for Kaposi sarcoma?**

A. Bronchoalveolar lavage

B. Transbronchial biopsy

C. Percutaneous needle biopsy of lung

D. Nothing further

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BOARD REVIEW DAY 4

#49 **A 21-year-old patient with HIV on bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) and history of adherence challenges resulting in intermittent low-level viremia presents to clinic. When lab results return, viral load has increased to 34,000 c/mL. The patient admits to discontinuing therapy because "he feels fine.". Genotypic resistance testing is ordered.**

How soon after discontinuation of antiretroviral therapy should resistance testing ideally be performed in order to detect drug resistance mutations?

A. Within 4 weeks

B. Within 3 months

C. Within 6 months

D. Within 12-18 months

1 of 2

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BOARD REVIEW DAY 4

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

The patient also has cryptosporidiosis with 6 stools per day plus considerable nausea and thus has limited food intake.

The pharmacy cannot obtain sulfadiazine or pyrimethamine.

What would be the best option for toxoplasmosis therapy?

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

1 of 2

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BOARD REVIEW DAY 4

#51 Which of the following is correct regarding primary prophylaxis for disseminated mycobacterium avium complex (MAC) disease?

A. Initiate primary prophylaxis if CD4 count is <50 cells/mm^3
B. Initiate primary prophylaxis if CD4 count is <100 cells/mm^3
C. Initiate primary prophylaxis if CD4 count is <200 cells/mm^3
D. Primary prophylaxis is not recommended for people with HIV who immediately initiate antiretroviral therapy

1 of 2

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BOARD REVIEW DAY 4

#52 A 72-year-old male living in a rural area of Southern New York State was admitted to the hospital in June with a five-day history of nausea, vomiting, headache, fever, somnolence, and confusion.

On examination, he had a temperature of 39°C, was oriented only to the person, had weakness in the right lower extremity, a faint maculopapular rash on his upper chest and back, and a right facial droop.

Routine laboratory tests were normal. LP: showed 108 WBC/mm^3 with 31% PMN, protein 113 mg/dl, and glucose 67 mg/dl. IgM serology for West Nile Virus on the CSF and serum was negative, as was the PCR for herpes simplex and West Nile virus.

MRI showed diffuse hyperintensity in the left basal ganglia on T2 and FLAIR imaging. He became progressively obtunded, requiring intubation for airway protection.

1 of 3

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BOARD REVIEW DAY 4

#52 According to his wife, he had been in good health and had returned two weeks before his illness from a camping trip with his family in a lake area in New Hampshire.

She said her husband had been concerned about finding a few ticks on his body while camping but had removed them the day he thought he had acquired them.

Which of the following agents is the most likely cause of this illness?

A. Varicella Zoster virus
B. Herpes simplex virus
C. Zika virus
D. Powassan virus
E. Enterovirus D68

2 of 3

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BOARD REVIEW DAY 4

#53 **Which of the following has demonstrated the greatest efficacy for HIV pre-exposure prophylaxis in women?**

A. Daily tenofovir alafenamide/emtricitabine
B. On-demand tenofovir disoproxil fumarate/emtricitabine (2-1-1 dosing)
C. Monthly intramuscular cabotegravir
D. Every 2-month intramuscular cabotegravir

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BOARD REVIEW DAY 4

#54 **A 49-year-old previously healthy female is referred to the ID clinic with 1-month of left sided neck swelling.**

Two weeks before the onset of symptoms, she found a tick embedded behind her left ear. She removed this without difficulty but developed an ulcerated area at the site of attachment (see arrow below).

Subsequently she developed left posterior auricular and posterior chain lymphadenopathy. A lymph node biopsy showed inflammatory changes with negative AFB and fungal stains.

She denies fevers or sore throat but does endorse fatigue.

1 of 4

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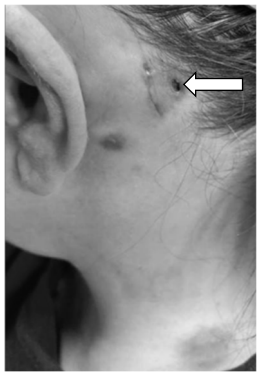
BOARD REVIEW DAY 4

#54 **She lives in a suburb of Nashville and works as a publicist. She has a pet dog and two cats, all of whom are healthy. She is an avid gardener and notes both rabbits and deer have been eating the planted vegetables. She denies sick contacts.**

Physical exam shows the lesions in the photo shown here.

Lab tests including CBC diff and CMP are both within normal limits.



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BOARD REVIEW DAY 4

#54 **What is the most likely cause of this patient's symptoms?**

A. Bartonella henselae
B. Kikuchi syndrome
C. Ehrlichia chaffeensis
D. Yersinia pestis
E. Francisella tularensis

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BR4 Board Review - Day 4
Moderator: Roy Gulick, MD

BOARD REVIEW DAY 4

#55 **A person with HIV who takes antiretroviral therapy as prescribed and achieves and maintains viral suppression will not transmit HIV to their sex partners (Undetectable = Untransmittable).**

Viral suppression in the context of treatment as prevention is defined by the Centers for Disease Control and Prevention as?

A. HIV-RNA level below the lower limit of detection of available assay

B. HIV-RNA level < 50 copies/mL

C. HIV-RNA level < 200 copies/mL

D. HIV-RNA level < 1000 copies/mL

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BOARD REVIEW DAY 4

#56 **A 24-year-old man newly diagnosed with HIV presents to care for rapid initiation of antiretroviral therapy. The patient previously received pre-exposure prophylaxis (PrEP) with intramuscular cabotegravir x 1 dose which was discontinued due to injection site reaction with subsequent use of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for PrEP. Baseline labs, including hepatitis B serologies and HIV resistance testing, are pending.**

Which of the following is an appropriate choice for rapid ART initiation?

A. Bictegravir/Tenofovir Alafenamide/Emtricitabine

B. Darunavir/Cobicistat/Tenofovir Alafenamide/Emtricitabine

C. Dolutegravir/Lamivudine

D. Doravirine/Tenofovir Disoproxil Fumarate/Emtricitabine

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BOARD REVIEW DAY 4

#57 **A 44-year-old male has noted about ten small skin and oral lesions appearing and growing slowly over several months. He feels well and has no other complaints. He is afebrile.**

He admits to multiple same sex partners over the past 20 years. He was aware of his HIV diagnosis several years ago but had never wanted to pursue therapy.

His physical examination and chest Xray are normal other than the skin and mucosal lesions.

Laboratory values are remarkable for positive HIV serology, CD4 count 400 cells/mm3, HIV viral load of 400,000 copies/mL. His routine hematology and chemistry blood work are normal.

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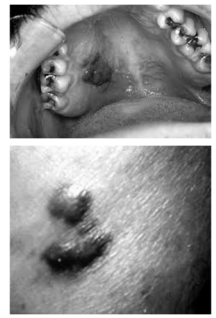
BOARD REVIEW DAY 4

#57 **Some of his lesions are shown here:**



https://phil.cdc.gov/Details.aspx?pid=6436

What diagnostic test(s) should you order to establish the cause and determine the therapy of these skin and mucosal lesions?

A. Skin biopsy only

B. Skin and mucosal biopsies

C. Skin biopsy and HHV 8 serology

D. Skin biopsy, serum HHV 8 PCR, and serum HHV 8 serology

E. No further test: the diagnosis of Kaposi sarcoma can be made clinically in this case

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BOARD REVIEW DAY 4

#58 A 36-year-old male with HIV, well controlled on antiretroviral therapy (TDF/FTC/DTG) for the last two years, presents to establish care at a new clinic.

He is requesting to switch to long-acting injectable therapy with Cabotegravir / Rilpivirine as a friend recently started this treatment with a high degree of satisfaction.

The patient's treatment history includes TDF/FTC/EFV which was discontinued due to poor tolerance and intermittent adherence; subsequent genotyping revealed a K103N mutation.

Other medical history includes methamphetamine use disorder (currently in remission) and depression (treated with escitalopram).

1 of 4

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BOARD REVIEW DAY 4

#58 Recent labs are as follows:

- HIV viral load < 20 copies per mL
- CD4+ T cell count 452 cells per cubic mL
- RPR non-reactive
- Hepatitis B surface antibody negative
- Hepatitis B core IgG positive
- Hepatitis B surface antigen positive
- Hepatitis B DNA viral load < 10 IU / mL
- Hepatitis C IgG negative
- Complete blood count, basic metabolic panel and liver function testing are all within normal limits.

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BOARD REVIEW DAY 4

#58 For this patient, which of the following would preclude switching to long-acting injectable therapy with cabotegravir /rilpivirine (LA CAB/RPV)?

A. History of treatment failure with TDF/FTC/EFV
B. K103N mutation
C. Current treatment with escitalopram
D. Positive Hepatitis B surface antigen
E. History of methamphetamine use disorder

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BOARD REVIEW DAY 4

#59 A 31-year-old woman is brought to the emergency department by her husband for fever and neurological symptoms.

She was completely well until 3 days earlier, when she felt nauseated and vomited twice.

During the next two days she had fever, felt "achy," developed a headache, and continued to have nausea and vomiting.

Upon awakening this morning, she complained of double vision, and her husband noted her eyes "weren't looking in the same place."

In the emergency room, she was found to have a temperature of 102.4°F. There was no rash. She had mild nuchal rigidity, right 6th cranial nerve palsy, and a sensory deficit over most of the left side of her body.

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BOARD REVIEW DAY 4

#59 **Her gait was very unsteady. The rest of the exam was unremarkable.**

An MRI of the head demonstrated inflammation of the pons and medulla.

Which one of the following organisms is the most likely cause of her illness?

A. Streptococcus pneumoniae

B. Nocardia nova

C. Mycobacterium tuberculosis

D. Listeria monocytogenes

E. Cryptococcus neoformans

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BOARD REVIEW DAY 4

#60 **A woman with HIV, a history of multiple antiretroviral regimens, and prior virologic failures is currently well controlled on a regimen of dolutegravir (DTG) once daily plus darunavir/cobicistat/tenofovir alafenamide/emtricitabine (DRV/c/TAF/FTC) once daily. She is now pregnant and presents for follow up.**

Which of the following statements is correct?

A. The patient is well controlled on the current regimen; continue standard treatment and monitoring measures

B. Tenofovir alafenamide is not recommended in pregnant individuals

C. Darunavir/cobicistat is not recommended in pregnant individuals

D. Darunavir/cobicistat dose should be increased from once daily to twice daily

1 of 2

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Tuesday, August 19, 2025

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Pharyngitis Syndromes Including Group A Strep Pharyngitis

Karen Bloch, MD

Pharyngitis Syndromes Including Group A Strep

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

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

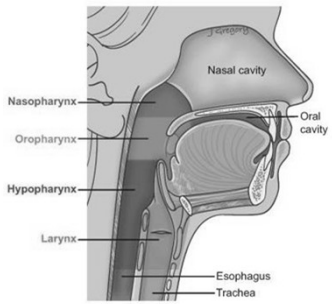
Special Thanks to Dr. Bennett Lorber!

2

Think Like A Realtor

3

Pharyngitis



- Micro-neighborhoods
- Regional differences

4

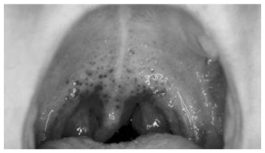
Question #1

38-year-old female presents with a 1 day of sore throat and fever.

Childhood history of anaphylaxis to penicillin.

Physical exam

- T=102.3
- HEENT-tonsillar erythema & petechiae
- Neck-Tender bilateral anterior LAN



Labs:

- Rapid strep antigen test negative

5

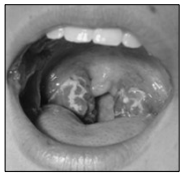
Question #1

What is the most appropriate antibiotic treatment?

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

6

Group A streptococcus



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

7

Differentiating Pharyngitis

GAS

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

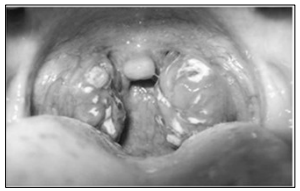
Viral pharyngitis

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

8

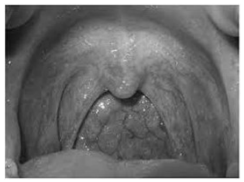
Differentiating Pharyngitis

GAS



vs

Viral pharyngitis



9

How Specific are Clinical Findings?

Modified CENTOR score

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

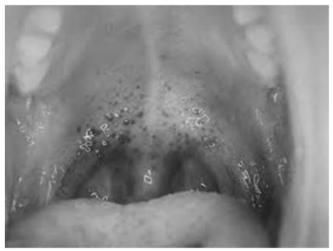
Points	Strep probability
0 or 1	< 10%
2	11 -17%
3	28 -35%
4 or 5	35-50%

IDSA guidelines recommend antibiotics only following a positive RADT testing.

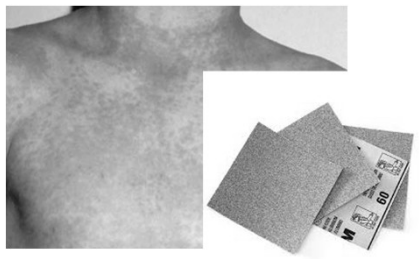
10

Streptococcal Clues

- Palatal petechia



- Scarletina



11

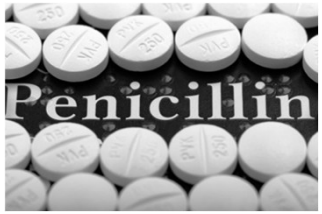
Laboratory Diagnosis

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

12

Treatment for GAS Pharyngitis

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



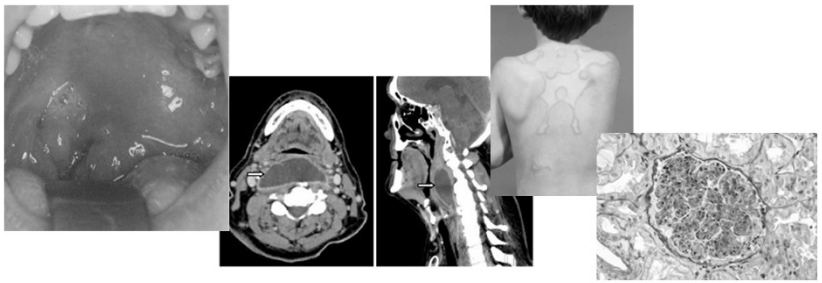
PCN Allergic:

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

13

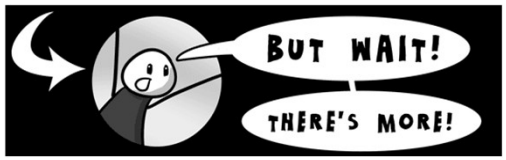
Secondary Complications

- Infectious complications
- Immunologic complications



14

Pharyngitis and….



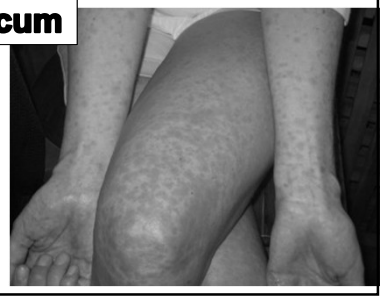
15

Pharyngitis & Rash

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

Arcanobacterium haemolyticum

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



16

Pharyngitis & Rash

- Acute HIV
- Secondary syphilis

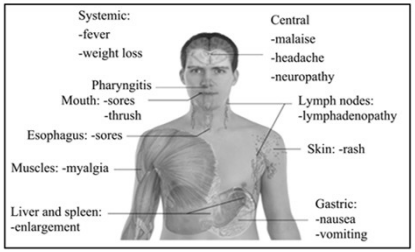
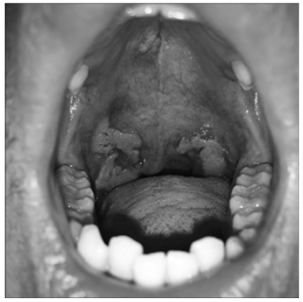


Figure 1 Main symptoms of acute HIV infection



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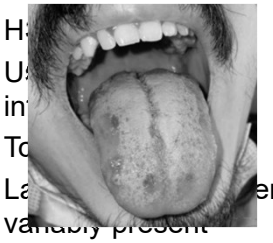
Pharyngitis after Receptive Oral Intercourse

Neisseria gonorrhoeae	**Herpes simplex virus**

- Highest risk MSM
- Diagnose by nucleic acid amplification test of pharyngeal swab

- H
- U
in
- To
- La ers
variably present



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Pharyngitis & Conjunctivitis

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

Adenovirus

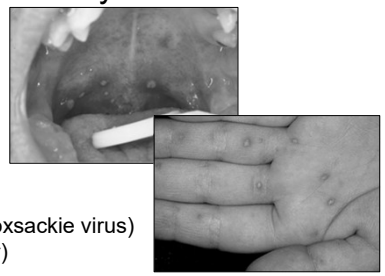
Epidemics in group living situations—barracks, dorms, camps, etc

19

Pharyngitis and Vesicles

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

Hand, Foot, and Mouth disease

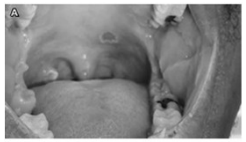


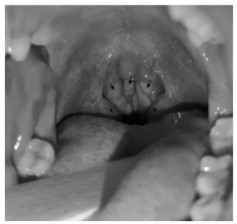
- Caused by enteroviruses (most common Coxsackie virus)
- More common in kids (often serve as vector)

20

Oral Lesions Due to Mpox

- Oral lesions often pre-date skin findings
- Seen in up to 25% of cases of mpox





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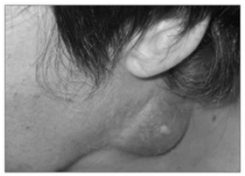
Question #2

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

22

Question #2

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



CMAJ 2014;186:E62

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Question #2

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

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

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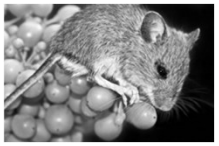
Oropharyngeal Tularemia

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



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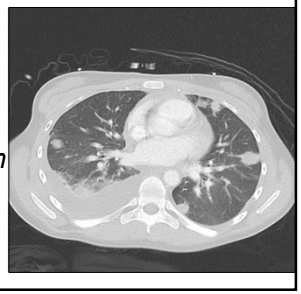
Pharyngitis and Chest Pain

- 20 yo college student with sore throat and fever. Despite oral amoxicillin, he develops new onset of cough and pleuritic CP; CT below

Lemierre syndrome

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



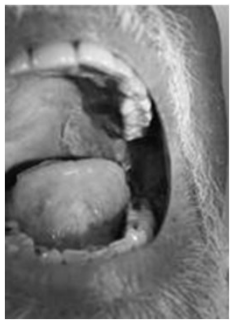
26

Pharyngitis in Immunocompromised Patients

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

Oropharyngeal Histoplasmosis

- Can mimic oral malignancy
- Denotes disseminated disease



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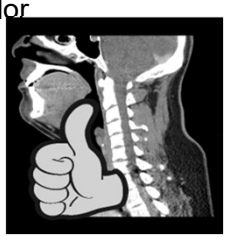
Extra-Tonsillar Infections: 1

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



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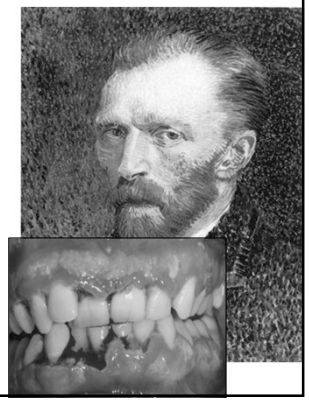
Extra-Tonsillar Infections: 2

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



29

Extra-Tonsillar Infections: 3

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

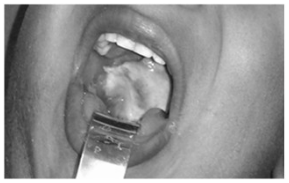
30

Question #3

PREVIEW QUESTION

- A 32-year-old woman is seen for a bad sore throat for 4 days
- Recently returned from her sister's wedding in Kazakhstan
- She c/o odynophagia and a low-grade fever

- T 100.2F; P 126; BP 118/74.
- HEENT: Submandibular swelling with gray exudate coating posterior pharynx.
  An S3 gallop is heard.
- EKG shows 1st degree AV nodal block, QT prolongation, and ST-T wave changes.



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Question #3

PREVIEW QUESTION

What is the most likely diagnosis?

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

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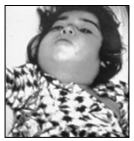
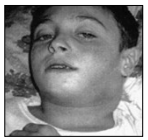
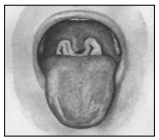
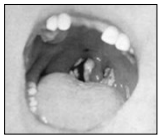
Buzz Words and Visual Associations

Bull neck:

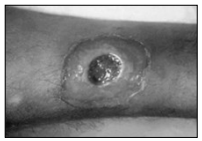

Grey pseudomembrane: extends onto palate or uvula; bleeds when scraped

33

Other Clues

- Location, location, location
  - Almost unheard of in developed countries (vaccination works!)
- Sore throat and myocarditis (~25%).
- Sore throat and neuropathies (~5%).
- Sore throat and cutaneous ulcer



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Noninfectious Mimics

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

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THANK YOU!

Karen.bloch@vumc.org

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Tuesday, August 19, 2025

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HIV-Associated Opportunistic Infections II

Rajesh Gandhi, MD

HIV-Associated Opportunistic Infections II

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

Acknowledgement: Dr. Henry Masur for slides

7/22/2025

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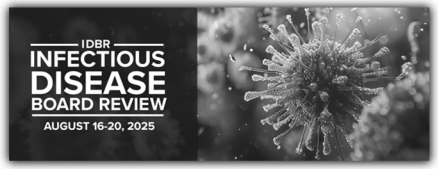


Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

HIV Associated Opportunistic Infections: Part 2

Opportunistic CNS Infections: Brain Lesions

Opportunistic CNS Infections: Cryptococcal Meningitis

Mycobacterial Infections

Immune Reconstitution Inflammatory Syndrome

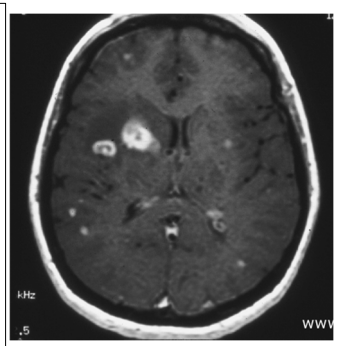
3

Question #1

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

What would you recommend?

A. Brain biopsy
B. Meningeal biopsy
C. Initiate anti-toxo therapy; if no response in 2 weeks, brain biopsy
D. Vancomycin, cefepime, metronidazole



4

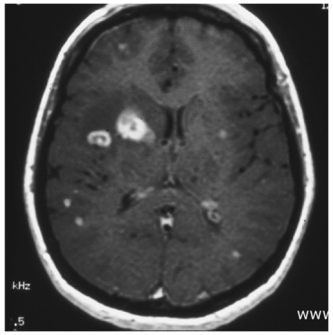
Brain Lesions in People with HIV (PWH)

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

Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

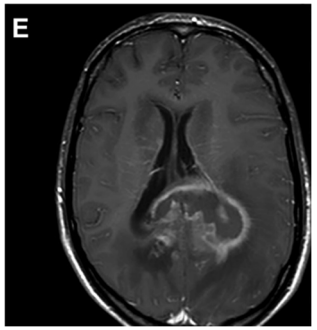
5

Toxoplasma Encephalitis



www.idimages.org

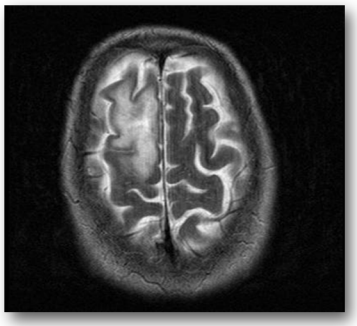
Primary CNS Lymphoma



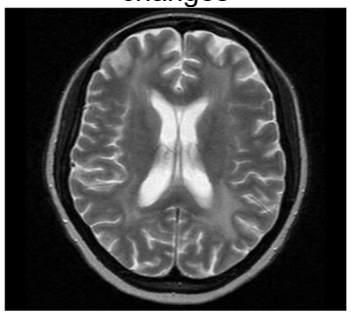
Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

6

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



HIV Encephalitis: bilateral symmetric white matter changes



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

7

Evaluation of CNS Mass Lesions in People with HIV/AIDS

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

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

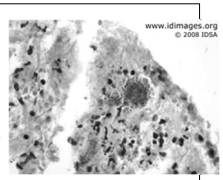
Laboratory Studies to Perform
- Serology: Toxo IgG
- Serum Cryptococcal Ag and Histoplasma Ag
- Blood culture - AFB
- CSF - Cryptococcal Ag
  - PCR (EBV, CMV, Toxoplasma, JC virus)

Response to Empiric Therapy

8

Toxoplasma Encephalitis (TE)

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

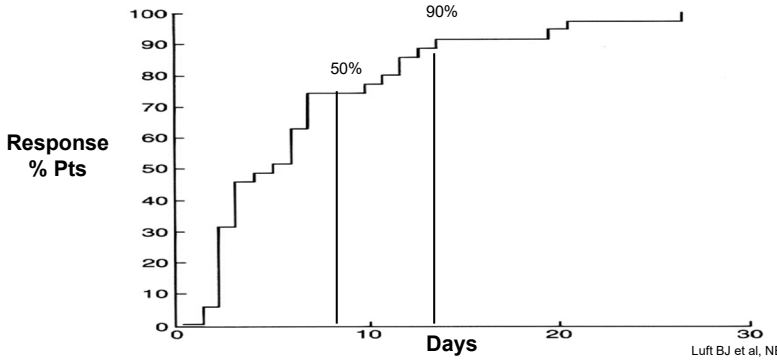


https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full

9

Time to Neurologic Response for Toxoplasma Encephalitis

35 PWH with TE Treated with Clindamycin - Pyrimethamine



Luft BJ et al, NEJM 1993

10

Therapy for Toxoplasma Encephalitis

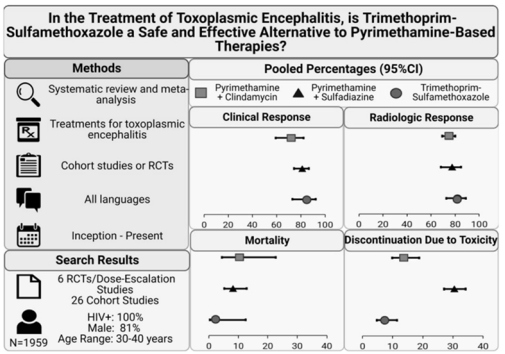
- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin (PO only)
    - May be unavailable or excessively expensive
  - Trimethoprim-sulfamethoxazole (PO or IV)
  - In patients with sulfa allergy, sulfa desensitization should be attempted
- **Alternative Regimens – for those who cannot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

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

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

11

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



Prosty C et al, Clinical Infectious Diseases, 2023

12

Adjunctive Therapies for Toxoplasma Encephalitis

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

13

Primary Prevention of Toxoplasmosis in People with HIV (PWH)

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

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

14

Primary Prevention of Toxoplasmosis in PWH

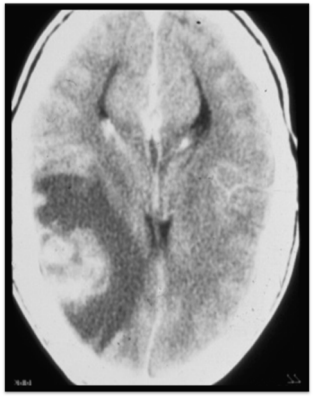
- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Nothing more is needed
- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine (plus leucovorin)
  - If on Aerosol pentamidine because cannot take TMP-SMX: not protected-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

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

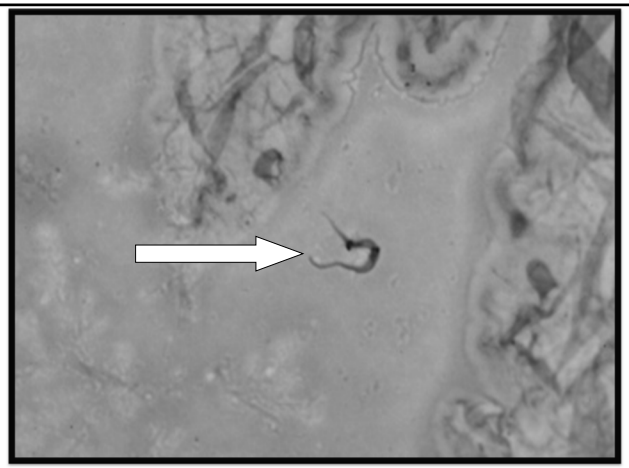
15

Case

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

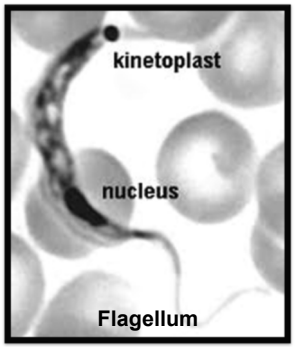


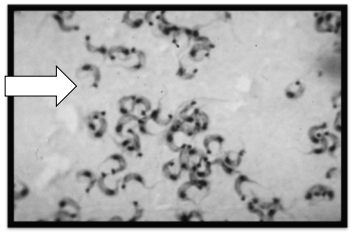
16



17

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





Badero et al, AIDS THERAPY, 4th Ed

DiazGranados C, Lancet ID, 2009

18

HIV Associated Opportunistic Infections: Part 2

Opportunistic CNS Infections: Cryptococcal Meningitis

19

Question #2

PREVIEW QUESTION

- 50-year-old woman with HIV (CD4 20, HIV RNA 500,000) presents with fever and headache. Not on antiretroviral therapy (ART). Diagnosed with cryptococcal meningitis
- Started on induction therapy (liposomal amphotericin plus 5FC)

When should she be started on ART?

A. Start ART at the same time as anti-fungal therapy
B. About 4 weeks after starting anti-fungal therapy
C. 6 months after starting anti-fungal therapy
D. After completing a full course of maintenance anti-fungal therapy

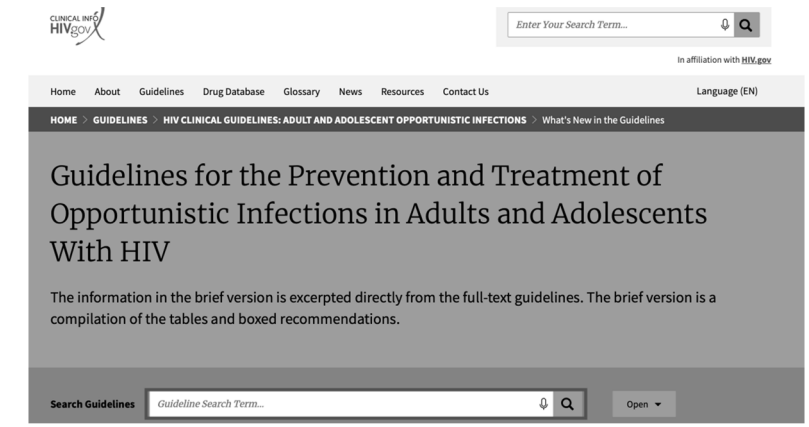
20

HIV-Associated Cryptococcal Meningitis

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

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

21



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

22

Therapy of Cryptococcal Meningitis

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

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

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

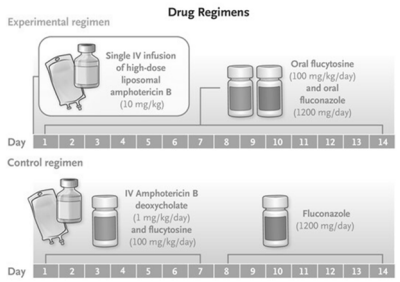
***** Stop after at least 1 yr total therapy if patient asymptomatic, CD4 >100, suppressed HIV RNA on ART**

23

Single-dose Liposomal AmB with Fluconazole/5FC

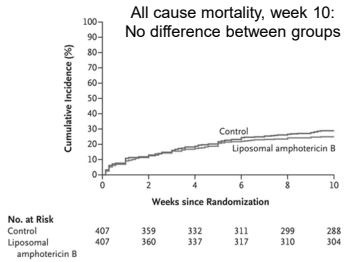
Preferred in resource-limited health care systems (WHO)

AMBITION Trial (n=814 participants)



Jarvis JN et al, NEJM, 2022

All cause mortality, week 10:
No difference between groups



Adverse events less frequent in single-dose AmB group

24

Management of Cryptococcal Meningitis - 1

- Patients should be followed in hospital for at least 7 days and ideally 14 days
- Lumbar puncture at day 7 and 14
- In patients with symptoms of elevated intracranial pressure and opening pressure >25 cm: remove CSF to reduce pressure by half or <20cm H20
  - Lumbar drain or VP shunt may be needed if pressures remain elevated
- Successful induction therapy = clinical improvement and negative CSF culture
- India ink and CSF CrAg frequently positive at Week 2: not indicative of failure
- Monitoring of cryptococcal antigen titers not recommended

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

25

Management of Cryptococcal Meningitis - 2

- For flucytosine, therapeutic drug monitoring indicated. Toxicities: marrow suppression, hepatitis, diarrhea. Renal elimination: monitor kidney function
- Not routinely recommended: Corticosteroids, Mannitol, Acetazolamide

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

26

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

ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

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

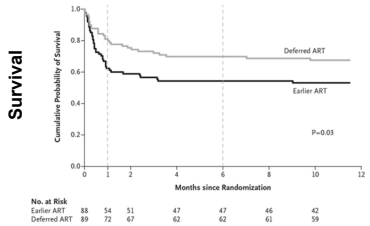
NEJM, 2016

27

When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines recommend ART initiation 4-6 weeks after initiation of antifungal therapy
- Some experts start ART at 2-4 weeks after initiation of anti-fungal therapy with ART initiation at 2 weeks for those who have clinically improved, have control of intracranial pressure, have negative CSF cultures and can be closely monitored

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



Boulware D et al, NEJM, 2014
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/cryptococcosis?view=full
Gandhi RT et al, IAS USA Guidelines, JAMA 2024

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

- **Screen patients with CD4 count <200 with serum cryptococcal antigen**
  - Frequency of + Ag: 2.9% if CD4 <100, 4.3% if CD4 < 50
  - Positive serum CrAg predicts development of disease
- **If Positive: Perform LP and Blood Cultures to determine Rx**
  - If CSF positive or serum CrAg by LFA is ≥1:640: Treat like cryptococcal meningitis/disseminated (Ampho/5FC)
  - If CSF negative: fluconazole 800 to 1200 mg daily for 2 wks, then 400 to 800 mg daily for 10 wks, then 200 mg daily (total 6 months)

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

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HIV Associated Opportunistic Infections: Part 2

Mycobacterial Infections

30

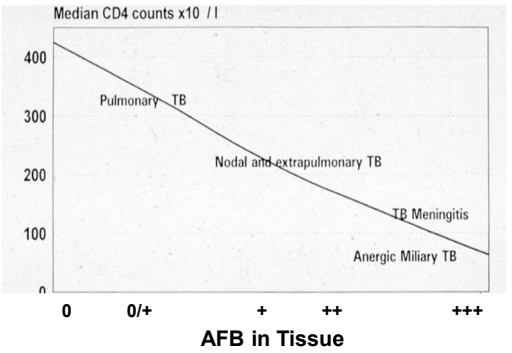
Tuberculosis in PWH: Highlights

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

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

31

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



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

32

Question #3

PREVIEW QUESTION

- 45-yo man with HIV (CD4 11, HIV RNA 300,000) presents with fever, diarrhea and weight loss.
- Started on dolutegravir + tenofovir/emtricitabine
- Two weeks later, develops enlarged supraclavicular lymph node
- Biopsy: necrotizing granulomas and AFB; cultures grow MAC

What would you recommend?

A. Stop ART and initiate treatment for MAC
B. Continue ART; initiate treatment for MAC
C. Start steroids and stop all other treatments

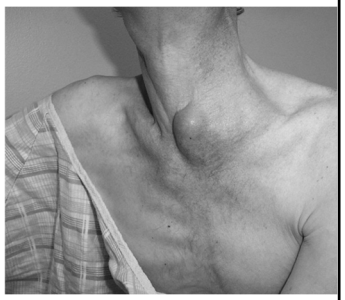


Image from Riddell J, J Translational Med, 2007

33

Mycobacterium Avium Complex

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

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

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Diagnosis

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

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

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Treatment for MAC

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

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

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~~Primary MAC Prophylaxis~~

- Primary prophylaxis against disseminated MAC disease is NOT recommended if ART initiated immediately
- People with HIV who have CD4 cell count <50, are not on ART, who remain viremic on ART or have no options for suppressive ART should receive prophylaxis after excluding disseminated MAC
  - Preferred agents: azithromycin (few drug interactions), clarithromycin

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

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HIV Associated Opportunistic Infections: Part 2

Immune Reconstitution Inflammatory Syndrome (IRIS)

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Definition:** Worsening manifestations or abrupt/atypical presentation of infection or tumor when ART started
  - Paradoxical: exacerbation of pre-existing infection or tumor
  - Unmasking: exacerbation of previously occult infection/tumor

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Predictors**
  - Pre therapy low CD4 cell count or high HIV RNA
  - Prior OI or recent initiation of therapy for OI
  - High pathogen load
- **Clinical Features**
  - Characterized by fevers and worsening of the underlying OI or tumor
  - May ”unmask” disease at previously unrecognized site or lead to paradoxical worsening of known OI
  - Usually occurs 4-8 weeks after ART initiation; may manifest earlier or later

40

Pathogens Commonly Associated with IRIS

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

41

Mycobacterial IRIS

PATHOGEN	TYPICAL/CHARACTERISTICS OF THE DISEASE
Mycobacterium tuberculosis	• Worsening lung infiltrates, lymphadenitis, CNS tuberculomas
MAC	• Lymphadenitis; pulmonary and abdominal disease. • Bacteremia generally absent. • Elevated alkaline phosphatase may be predictive. • Severe forms of MAC IRIS with hemophagocytic lymphohistiocytosis phenotype may occur

Cecil Medicine Textbook (French and Meintjes)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

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Examples of IRIS

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

Cecil Medicine Textbook (French and Meintjes)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

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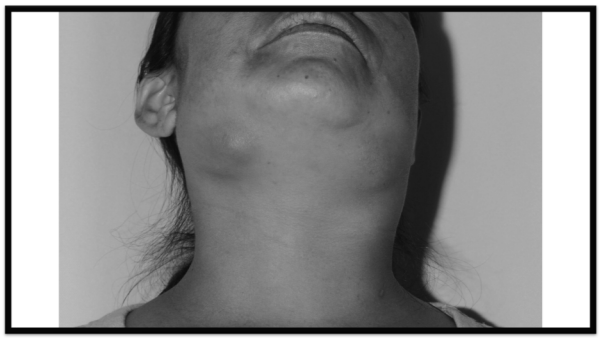
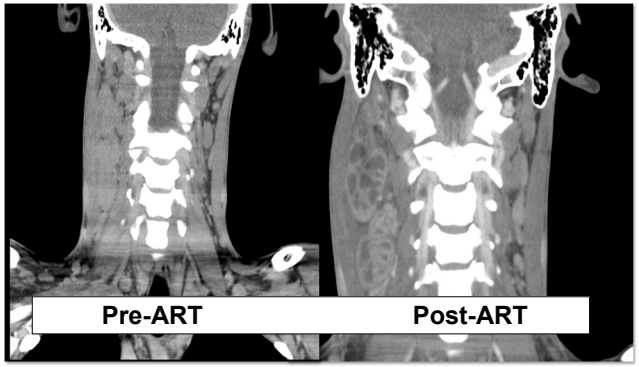
Immune Reconstitution Inflammatory Syndrome (Mycobacterium avium complex)



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

44

MAC IRIS in Patient with HIV



Sereti I, IAS USA Topics in Antiviral Medicine, 2019

45

Management of IRIS

- **Reassess Diagnosis**
  - Evaluate for concurrent, additional OIs and tumors
- **Treat IRIS**
  - Continue ART
  - Continue treatment of identified pathogen
  - NSAIDS or Corticosteroids

46

Summary

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

New guidelines for induction, consolidation and maintenance therapy for cryptococcal meningitis; deferring ART for about 2-4 weeks appropriate

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

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

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Tuesday, August 19, 2025

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Syndromes Masquerading as Infections

Karen Bloch, MD

Syndromes that Masquerade as Infections

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7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Special Thanks to Dr. Bennett Lorber!

2

ID Board Content

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

3

Mimics

- Many conditions masquerade as infections
  - Fever almost universally present
  - Sometimes focal abnormality
    - Cellulitis vs stasis dermatitis
    - Viral vs Organizing Pneumonia
    - Lymphadenitis vs Lymphoma

VS

4

Test Taking Tip

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

5

Test Taking Tip

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

(Pulmonary) TULAREMIA

6

Test Taking Tip

If I say, “chitterlings” (aka chitlins, aka hog intestines)

You say…..

7

Test Taking Tip

If I say, “chitterlings”

You say…..

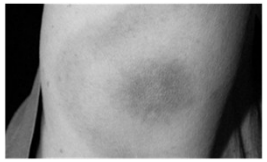
YERSINIA (gastroenteritis)

8

Test Taking Tip

If I say, ”Bull’s-eye rash”

You say…..

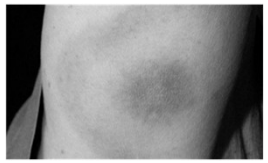


9

Test Taking Tip

If I say, ”Bull’s-eye rash”

You say…..



Lyme disease
(or Erythema migrans or STARI)

10

My Approach to Mimics

- Think like an Internist
- The key is recognition, not treatment
- This talk will emphasize illustrative cases
- Goal is to cover lots of non-infectious diseases rather than in-depth discussion using buzzwords for easy recognition!

11

Examples

12

Question #1

A young man has oral and genital ulcers. You suspect Behçet's disease.

Which of the following is most consistent with that diagnosis?

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

13

Question #2

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

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

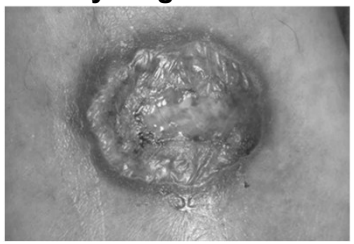
14

Question #3

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

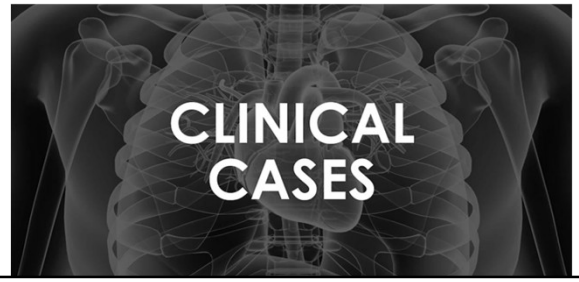
Which of the following is the most likely diagnosis?

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



15

But this being boards…



To optimize learning: CLOSE THE SYLLABUS

16

Question #4

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

17

Question #4

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

18

Question #4

What is the most appropriate next study?

A. Flow cytometry of whole blood
B. ANA profile
C. CMV PCR
D. Soluble IL-2 receptor level
E. Toxoplasma titer

19

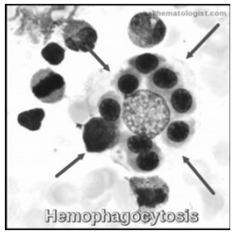
Hemophagocytic Lymphohistiocytosis

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

20

HLH-2024: Diagnostic Criteria

- At least **5/7** of the following:
  - Fever (T>38.5°C)
  - Splenomegaly
  - Cytopenias (2/3 lineages)
  - Hypertriglyceridemia (>3mmol/L)
  - Ferritin >500 mcg/mL
  - Elevated soluble IL-2 receptor (aka sCD25)



Note: NK cell function now a functional criteria

21

HLH Clues

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

22

Question #5

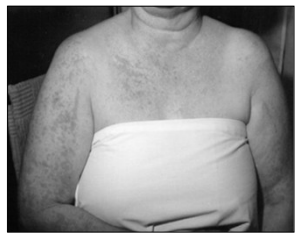
- A 39-year-old woman is admitted for fever of 3 weeks associated with diffuse arthralgias involving the knees, wrists and ankles.
- A severe sore throat was present during the first week of the illness but has resolved.

23

Question #5

Physical Exam

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



24

Question #5

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

25

Question #5

What is the most likely diagnosis?

A. Lymphoma
B. Adult Still's Disease
C. Acute Rheumatic Fever
D. Cryoglobulinemia
E. Kikuchi Disease

26

Adult Still's Disease (Adult Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

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

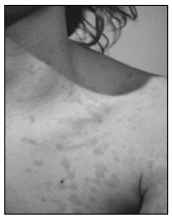
27

Adult Still's Disease

- Buzzwords and associations:

Evanescent, **salmon-colored** rash

=



Koebner phenomenon (rash at pressure sites)

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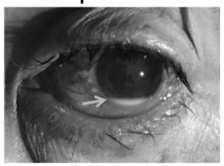
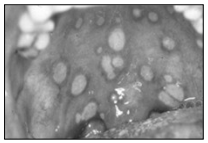
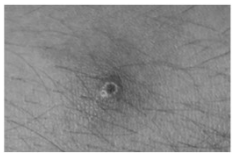
Question #6

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

29

Question #6

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

30

Question #6

What is the most likely diagnosis?

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

31

Behçet's Disease

Pleomorphic vasculitis diagnosed clinically

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

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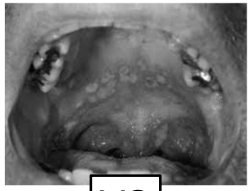
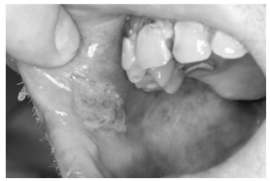
Behçet's Disease



VS

- Ulcers is the buzzword, but the trick is differentiation from infectious causes (HSV, coxsackie, etc.)



- Additional Clues
  - Recurrence
  - Ocular findings
  - Pathergy (needle or IV site)

33

Question #7

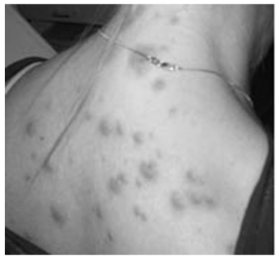
- A 38-year-old woman with AML is admitted with fever. She underwent induction chemotherapy 2 weeks prior, complicated by neutropenic fever that resolved with marrow recovery
- She presents with a 1-day history of fever without localizing symptoms
- Exam: T 101.4°F; P 98; otherwise, unremarkable
- CBC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

34

Question #7

Hospital Day 2:

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



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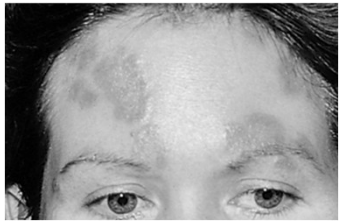
Question #7

Hospital Day 3:

- Fever persists; some of the papules develop a plaque-like appearance

Hospital Day 4:

- Skin biopsy with dense perivascular infiltrates of neutrophils without evidence of vasculitis; stains for organisms negative



36

Question #7

Which is the most likely diagnosis?

A. Ecthyma gangrenosum
B. Pyoderma gangrenosum
C. DRESS
D. Leukemic infiltrates
E. Sweet syndrome

37

Sweet Syndrome

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

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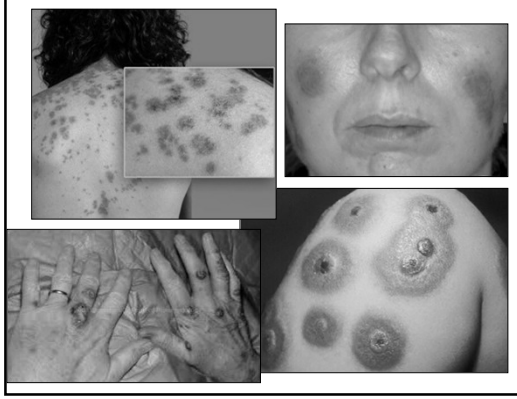
Skin Lesions in Sweet Syndrome

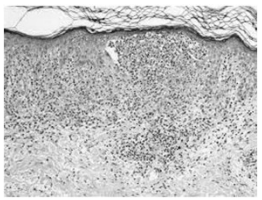


- Lesions appear **abruptly** and usually **tender**
- May be single or multiple, often involving **dorsum of hand**
- Red, violaceous, or yellow center
- Nodular or **plaque-like**
- Central umbilication with **target appearance**

39

Sweet Syndrome

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



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

40

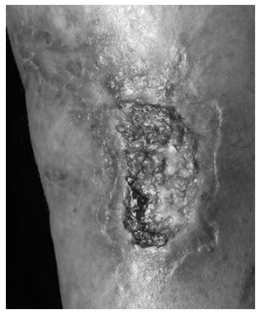
Question #8

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

41

Question #8

- Exam:
  - T 100.2°F
  - Abdo pain to palpation
  - Skin lesion
- Labs:
  - WBC 11,150 (2% eos)
  - ESR=79, CRP=110
  - BMP normal
  - Chest x-ray normal



42

Question #8

Which one of the following is the most likely diagnosis?

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

43

Pyoderma gangrenosum

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

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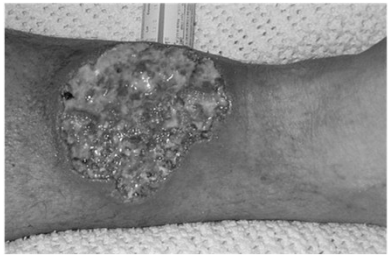
Pyoderma gangrenosum

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



45

Question #9

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

46

Question #9

- Exam:
  - T 102.2°F, P 104, BP 124/84
  - Slight tenderness over left scalp
  - Mitral regurgitant murmur
  - Rest of exam normal
- Labs:
  - Hb 9.8; WBC 9800, normal diff
  - UA normal
  - Basic metabolic panel normal
  - Sedimentation rate 147

47

Question #9

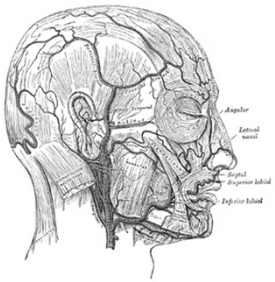
Which of the following is most likely to be diagnostic?

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

48

Giant Cell Arteritis

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



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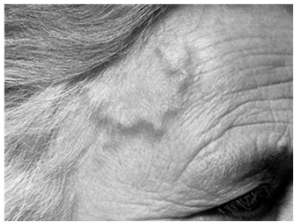
Giant Cell Arteritis



Buzzwords & Associations:

FUO in a patient >50 years PLUS

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

50

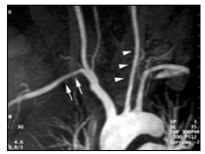
Overlap of GCA and PMR

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

51

Takayasu Arteritis

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



52

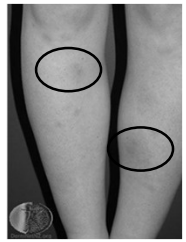
Question #10

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

53

Question #10

- Exam:
  - T 100.5°F; Pulse 72; BP 110/70
  - Bilateral synovial thickening of ankles with warmth and tenderness to passive movement
  - Skin exam with painful pre-tibial nodules
- Labs:
  - WBC 8.8 (76% segs)
  - CRP=167
  - Uric acid=4.4
  - RF <15, Anti-CCP Ab negative



54

Question #10

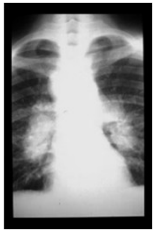
Which of the following is most likely to be diagnostic?

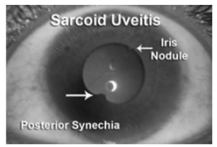
A. Chest x-ray
B. Serology for *Borrelia burgdorferi*
C. Urine *Histoplasma* antigen
D. Arthrocentesis
E. Skin biopsy

55

Sarcoidosis

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

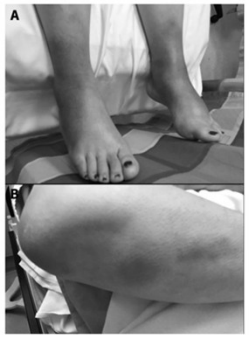




56

Erythema nodosuma

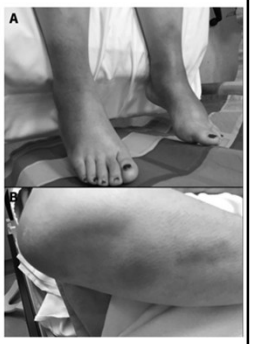
- No cause >50% of cases
- Drugs: sulfonamides, penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's)
- Microbes:
  - EBV, Hep B/C
  - *Streptococci*, *Bartonella,* TB
  - Endemic fungi



57

Erythema nodosuma

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



58

Question #11

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

- A 19-year-old Iraqi immigrant is hospitalized for 2-day history of fever and abdominal pain.
- He has had similar episodes on at least 3 previous occasions over the past 7 years. At the first episode he underwent appendectomy; the appendix path was normal. Subsequent episodes resolved spontaneously after 2-3 days.
- Exam:
  - T 102.2°F; pulse 114; no rash
  - Abdominal guarding, rebound tenderness, hypoactive bowel sounds
- Labs:
  - WBC 16,650; UA normal
  - BMP & LFTs normal
  - No occult blood in stool
  - CT of abdomen and pelvis normal

59

Question #11

PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

What is the most likely diagnosis?

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

60

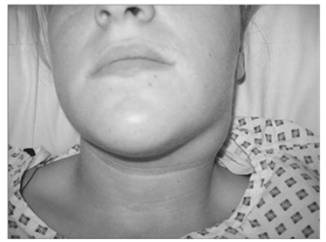
Familial Mediterranean Fever

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

61

Question #12

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



62

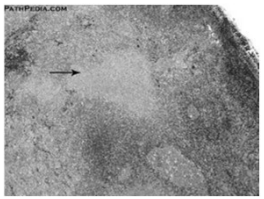
Question #12

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

63

Question #12

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



64

Question #12

Which one of the following is the most likely diagnosis?

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

65

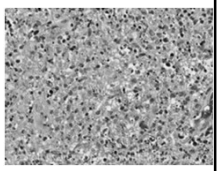
Kikuchi Disease

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

66

Kikuchi Disease

- Diagnosis by pathology:
  - Necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris



- Buzzwords and associations:
  - Acute onset fever and cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis

67

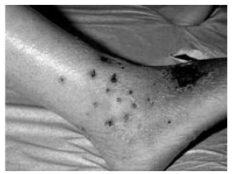
Question #13

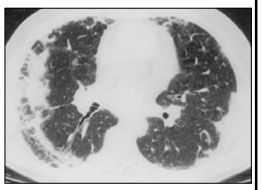
- A 41-year-old woman is seen for fever, worsening respiratory symptoms, and a rash.
- She has long-standing asthma with frequent exacerbations.
- She uses an inhaler several times a day and was recently placed on a leukotriene receptor antagonist. She is being tapered off steroids which she has taken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

68

Question #13

- Exam: Temp 101.5°F; RR 24
- Diffuse wheezing; palpable purpura with nodules on elbows and legs
- Labs: WBC 15,230 (22% eosinophils)
- CT scan: bilateral peripheral infiltrates
- Skin nodule biopsy: granulomas





69

Question #13

Which one of the following is the most likely diagnosis?

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

70

EGPA

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

71

EGPA

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

72

Question #14

PREVIEW QUESTION

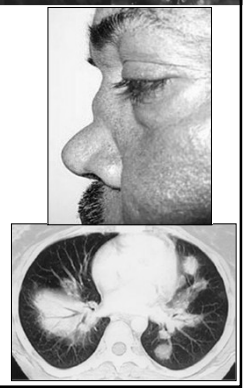
- A 38-year-old man is seen for a 6-week history of cough, intermittent fever and night sweats
- He has had nasal stuffiness for 4-5 months with occasional epistaxis
- He lives in Philadelphia, and 6 months ago traveled to Cincinnati on business
- He has no pets and takes only an OTC decongestant. He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

73

Question #14

PREVIEW QUESTION

- Exam:
  - T 100.2°F; RR 18;
  - Nasal deformity with perforation of septum
  - Lungs clear; rest of exam normal
- Labs:
  - WBC 6,900 with normal differential
  - UA 30-50 RBC; BMP normal
  - Chest CT: bilateral nodules with cavitation



74

Question #14

PREVIEW QUESTION

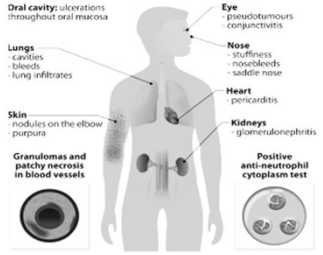
Which of the following will most likely support the diagnosis?

A. c-ANCA
B. Anti-glomerular basement membrane Ab
C. Urine toxicology screen
D. Angiotensin converting enzyme (ACE)
E. Pulmonary angiogram

75

Granulomatosis with Polyangiitis (GPA)

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



76

Granulomatosis with Polyangiitis (GPA)

Dx:

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

Buzzwords and associations:

Nasal symptoms (Saddle nose and perforation)
Lung nodules
Respiratory and renal findings (hematuria)

77

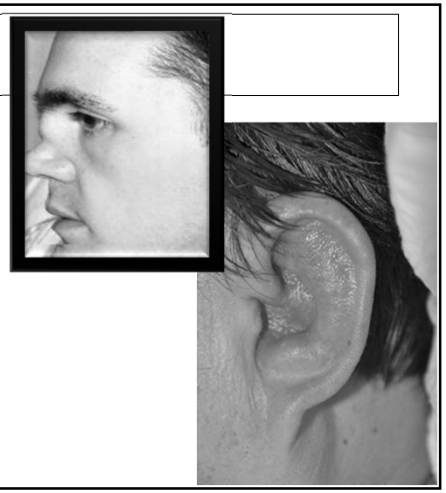
Question #15

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

78

Question #15

- Exam:
  - Afebrile
  - Left auricle is inflamed and tender, ear lobe is spared
  - He has a saddle-nose deformity; the nasal mucosa is normal
  - Labs: CBC normal



79

Question #15

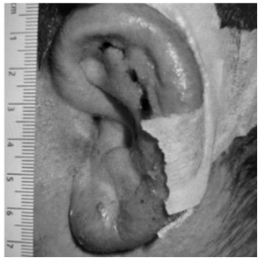
What is the most likely diagnosis?

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

80

Relapsing Polychondritis

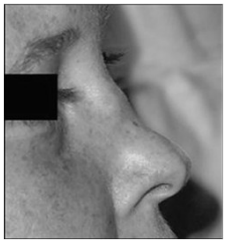
- Immune-mediated condition
- Inflammation of cartilaginous structures, particularly ears, but also nose, eyes, joints, and airways
- Clinical diagnosis



81

Saddle-nose Deformity

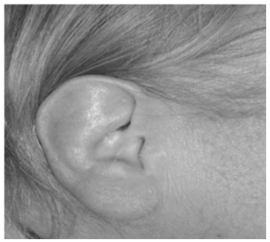
- Granulomatosis with polyangiitis
- Relapsing polychondritis
- Lepromatous leprosy
- Congenital syphilis
- Leishmaniasis
- Cocaine use



82

Relapsing Polychondritis

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



83

Karen.bloch@vumc.org

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Tuesday, August 19, 2025

42

Non-AIDS-Defining Complications of HIV/AIDS

Michael Saag, MD

Non-AIDS Defining Complications of HIV/AIDS

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

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Question #1

PREVIEW QUESTION

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

3

Question #1

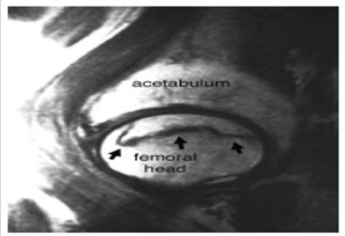
PREVIEW QUESTION

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

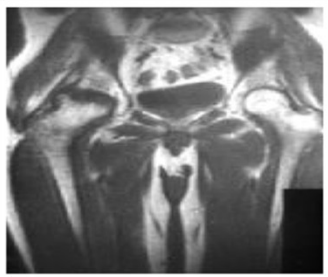
A. Osteonecrosis of femoral head
B. Fanconi syndrome
C. Vitamin D deficiency
D. Tenofovir bone disease
E. Hypogonadism

4

Osteonecrosis



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



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

5

Avascular Necrosis in HIV

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

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

6

Question #2

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

7

Question #2

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

8

Question #2

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

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

9

Question #2

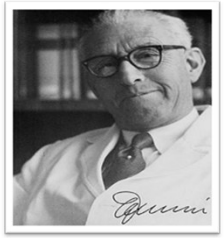
Which of the following is the most likely diagnosis?

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

10

Fanconi Syndrome

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



11

Question #3

PREVIEW QUESTION

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

12

Question #3

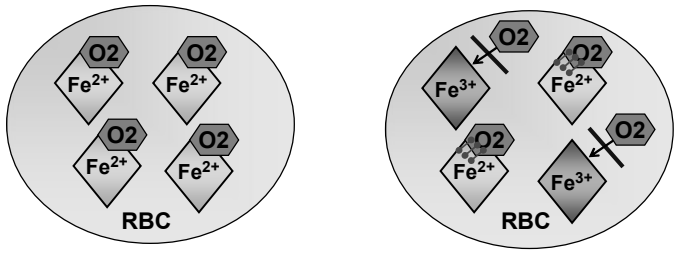
PREVIEW QUESTION

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

A. Recurrent PCP
B. IRIS reaction
C. Drug toxicity
D. Pulmonary embolus
E. Patent foramen ovale

13

Hemoglobin and Methemoglobin



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Question #4

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

A. Yes
B. No
C. Not sure

15

REPRIEVE Study (Started in 2015)

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

16

Question #5

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

17

Question #5

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

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

18

Question #6 (Bonus)

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

A. An ACE inhibitor
B. Corticosteroids
C. High molecular weight Dextran
D. Antiretroviral therapy
E. A calcium channel blocker

19

Question #7

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

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

Rare schizocytes on peripheral blood smear

20

Question #7

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

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

21

Question #8

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

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

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

22

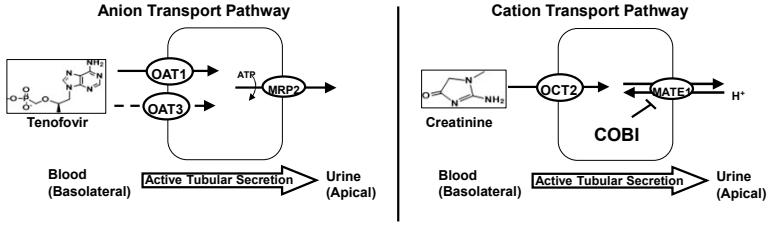
Question #8

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

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

23

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

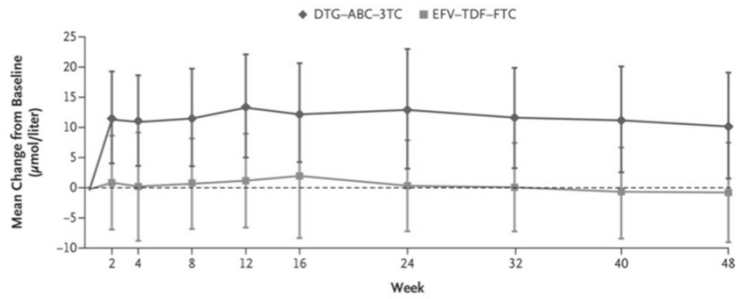


The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

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

24

Changes in eGFR



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

25

Question #9

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

26

Question #9

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

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

27

IRIS

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

28

Question #10

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

29

Question #10

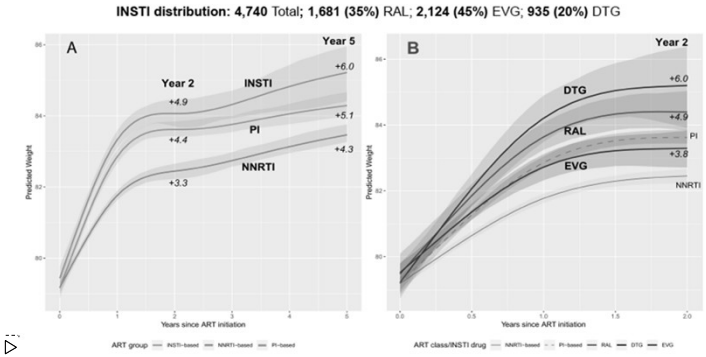
Which of the following will most likely be present on his 3 month visit from use of dolutegravir?

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

30

Change in Weight Overtime – NA-ACCORD

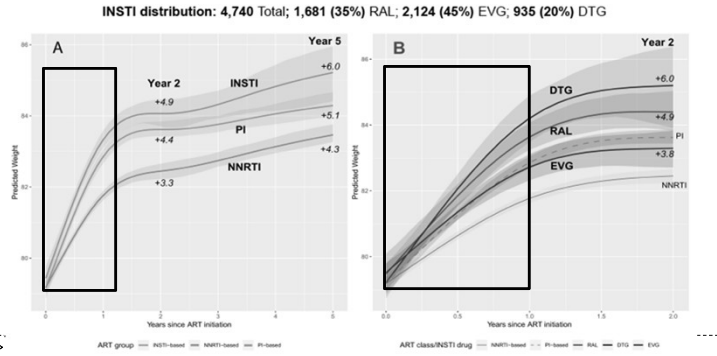
Bourgi et al CROI 2019



31

Change in Weight Overtime – NA-ACCORD

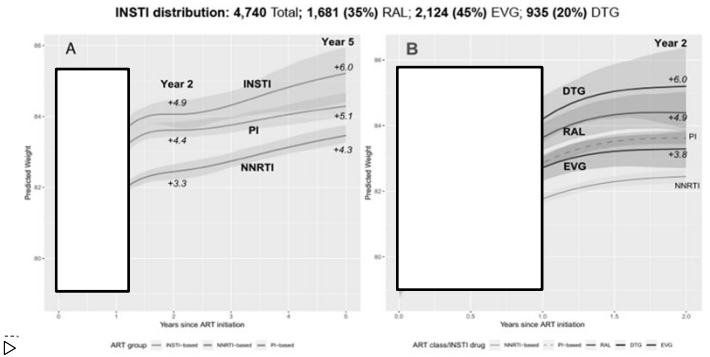
Bourgi et al CROI 2019



32

Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



33

Question #11

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

34

Question #11

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

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

35

U=U: Undetectable=Untransmittable

https://www.preventionaccess.org/about
https://www.health.ny.gov/diseases/aids/ending_the_epidemic/
https://www.cdc.gov/hiv/library/dcl/dcl/092717.html

36

Question #12

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

37

Question #12

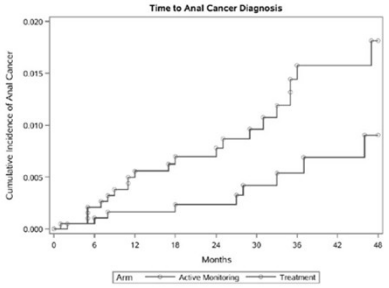
Which of the following should be performed?

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

38

Treatment of HSIL Reduces Risk of Anal Cancer By 57%

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



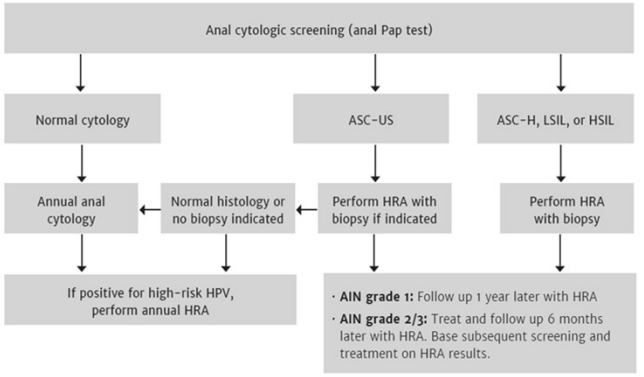
Anal dysplasia

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

39

Figure 1. Follow-up of Anal Cytologic Screening Results

CLINICAL GUIDELINES PROGRAM



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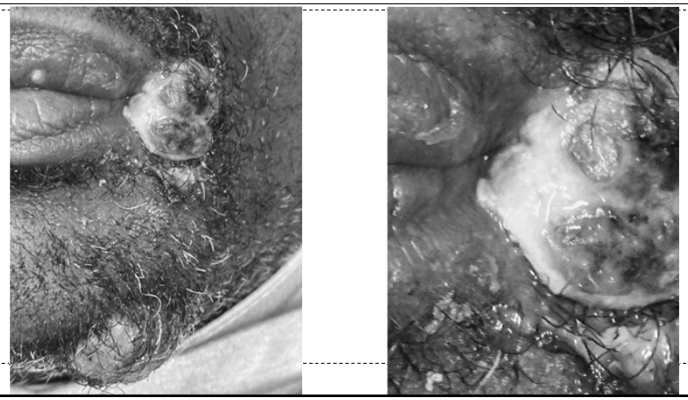
Recommendations: Screening

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

Question #13

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

Question #13



Question #13

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

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

- **Contact me:**
  msaag@uabmc.edu

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Tuesday, August 19, 2025

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Bacterial and Viral Meningitis

Allan Tunkel, MD

Viral and Bacterial Meningitis

Allan R. Tunkel, MD, PhD, MACP

Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

7/22/2025

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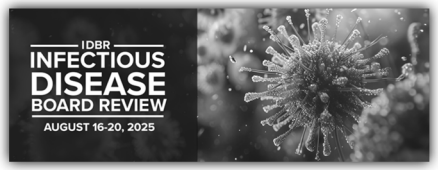


Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Question #1

PREVIEW QUESTION

3

- 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 99.8^{o}F 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

3

Question #1

PREVIEW QUESTION

4

Which of the following is the most likely etiology of this patient's meningitis?

A. Coxsackie A virus
B. Coxsackie B virus
C. Parvovirus B19
D. Herpes simplex virus type 2
E. Human herpesvirus 6

4

Viral Meningitis
Major Etiologies

5

- Enteroviruses
- Mumps virus
- Herpesviruses
- Lymphocytic choriomeningitis virus
- Others
  - Arboviruses
  - Human immunodeficiency virus
  - Adenovirus
  - Parainfluenza virus types 2 and 3

5

Cerebrospinal Fluid (CSF) Findings in Viral Meningitis

6

CSF Parameter	CSF Findings
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

6

Enteroviruses

7

- 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

7

Enteroviruses

8

- 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

8

Enteroviruses

9

- 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

9

Mumps Virus

10

- 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%)

10

Herpes Simplex Virus

11

- 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

11

Herpes Simplex Virus

12

- Diagnosis
  - Lymphocytic pleocytosis (<500 cells/mm^3); normal glucose, elevated protein
  - CSF PCR
- Therapy
  - Usually self-limited; unclear if antiviral therapy alters course of mild meningitis, but usually recommended
  - Suppressive therapy (valacyclovir) not indicated for recurrent disease; associated with a higher frequency of meningitis after cessation of active drug

12

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

13

Question #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

14

Question #2

15

- Presented 1 month later with headache, meningismus and altered mental status, and a temperature of T 39^{o}C
- Lumbar puncture had WBC 2500/mm^3 (98% neutrophils), glucose 20 mg/dL, and protein 450 mg/dL
- Placed on empiric antimicrobial therapy with vancomycin, ampicillin, and ceftriaxone
- Cultures of blood and CSF grew *Escherichia coli*

15

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

16

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%)

17

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

18

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

19

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

20

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

21

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

22

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

23

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

24

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

25

Meningitis/Encephalitis Panel

26

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

26

Question #3

27

- A 25-year-old man presents to the hospital with a 2-day history of fever, chills, headache, and mild confusion. He has paroxysmal nocturnal hemoglobinuria and is currently on therapy with ravulizumab; he also takes oral penicillin V daily. Prior to starting ravulizumab; he received the quadrivalent (ACWY) meningococcal conjugate vaccine and the serogroup B meningococcal vaccine.
- T 40.5°C, P 120, RR 28, BP 90/60 mmHg; obtunded, stiff neck
- WBC 30,000/mm^3 (40% bands), platelets 40,000/mm^3
- Lumbar puncture revealed an opening pressure of 300 mm H_2O, WBC 1500/mm^3 (99% segs), glucose 20 mg/dL, and protein 300 mg/dL

27

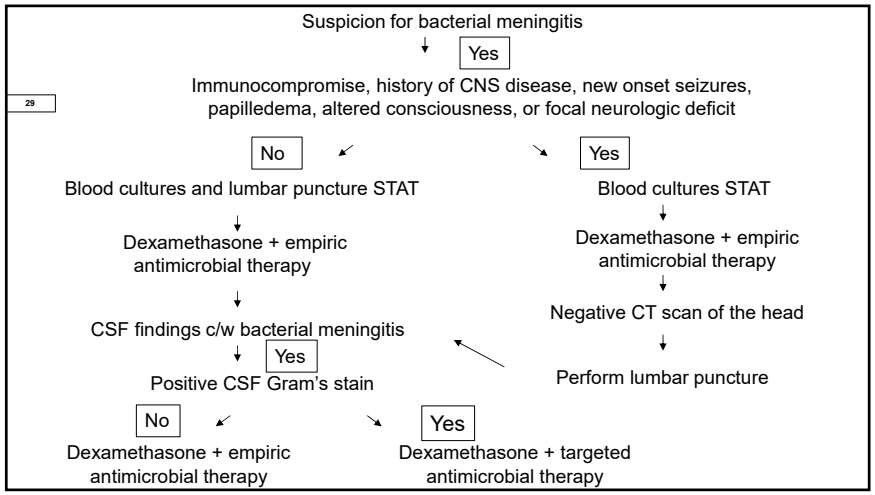
Question #3

28

Which of the following empiric antimicrobial regimens should be initiated?

A. Penicillin G
B. Ceftriaxone
C. Vancomycin + ampicillin
D. Vancomycin + ceftriaxone

28



29

Empiric Antimicrobial Therapy of Purulent Meningitis

30

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

30

Empiric Antimicrobial Therapy of Purulent Meningitis

31

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

Targeted Antimicrobial Therapy in Bacterial Meningitis

32

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

32

Pneumococcal Susceptibility to Penicillin

33

33

Pneumococcal Susceptibility to Penicillin

34

	Minimal Inhibitory Concentration
Susceptible	≤0.06 mg/mL
Resistant	≥0.12 mg/mL

34

Antimicrobial Therapy in Bacterial Meningitis

35

Organism	Antimicrobial Therapy
Streptococcus pneumoniae	
PCN MIC ≤0.06 mg/mL	Penicillin G or ampicillin
PCN MIC ≥0.12 mg/mL	
CTX[a] MIC <1.0 mg/mL	Third-generation cephalosporin[a]
CTX[a] MIC ≥1.0 mg/mL	Vancomycin + a third-generation cephalosporin[a,b]

[a]ceftriaxone or cefotaxime
[b]consider addition of rifampin if ceftriaxone MIC ≥4 mg/mL

35

Antimicrobial Therapy in Bacterial Meningitis

36

Organism	Antimicrobial Therapy
Neisseria meningitidis	
PCN MIC <0.1 mg/mL	Penicillin G or ampicillin
PCN MIC 0.1-1.0 mg/mL	Third-generation cephalosporin[a]
Haemophilus influenzae	
b-lactamase-negative	Ampicillin
b-lactamase-positive	Third-generation cephalosporin[a]

[a]ceftriaxone or cefotaxime

36

Antimicrobial Therapy in Bacterial Meningitis

37

Organism	Antimicrobial Therapy
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Acinetobacter baumannii	Meropenem or colistin (formulated as colistimethate sodium)[a] or polymyxin B[a]
Streptococcus agalactiae	Ampicillin or penicillin G
Listeria monocytogenes	Ampicillin or penicillin G[b]
Staphylococcus aureus	
MSSA	Nafcillin or oxacillin
MRSA	Vancomycin

[a]also administered by intraventricular or intrathecal routes
[b]addition of an aminoglycoside should be considered

37

Question #4

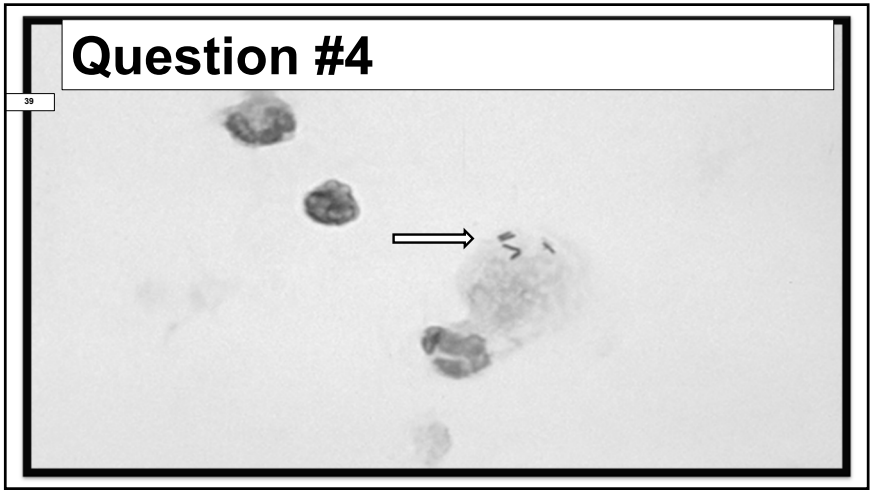
38

- 60-year-old male with chronic lymphocytic leukemia presented with fever, headache, ataxia, and altered mental status. Recently traveled to an outdoor family picnic in rural Virginia. He is allergic to penicillin (anaphylaxis)
- T 102°F, P 120, RR 24, BP 100/60 mmHg
- He was obtunded and had nuchal rigidity
- WBC was 25,000/mm^3 (30% bands)
- LP revealed a WBC 1500/mm^3 (50 neutrophils, 50% lymphocytes), glucose 30 mg/dL, and protein 200 mg/dL

38

Question #4

39



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Question #4

40

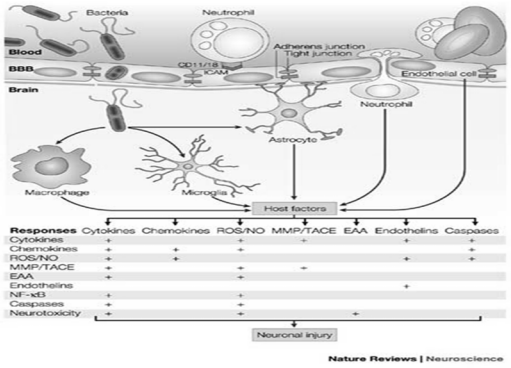
Which of the following antimicrobial regimens should be initiated?

A. Vancomycin
B. Trimethoprim-sulfamethoxazole
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

40

Adjunctive Dexamethasone in Bacterial Meningitis

41



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Adjunctive Dexamethasone in Bacterial Meningitis

42

- 301 adults with bacterial meningitis ≥17 years of age
- Randomized, double blind, placebo-controlled
- Dexamethasone (0.15 mg mg/kg q 6 hr for 4 days) given 15-20 minutes before first antimicrobial dose
- All patients: reduction in unfavorable outcome (15 vs 25% P=0.03) and mortality (7 vs 15%; P=0.04)
- Pneumococcal meningitis: reduction in unfavorable outcome (26 vs 52%; P=0.006) and mortality (14 vs 34%; P=0.02)

de Gans and van de Beek. N Engl J Med 2002;347:1549

42

Adjunctive Dexamethasone in Bacterial Meningitis

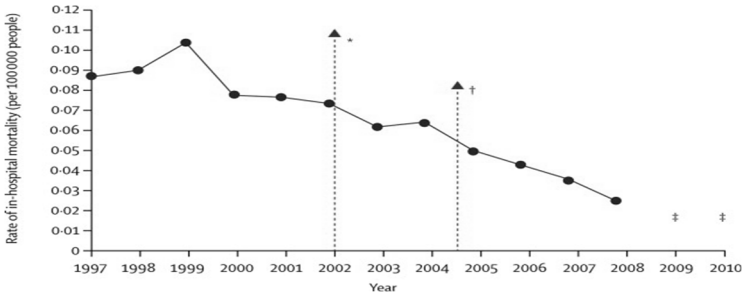
43

- 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 bacterial meningitis
- Administer at 0.15 mg/kg IV every 6 hours for 4 days in adults concomitant with or just before first antimicrobial dose; European guidelines endorse use up to 4 hours after antimicrobial therapy

43

In-Hospital Mortality for Pneumococcal Meningitis

44



Castelblanco et al. Lancet ID 2014;14:813

44

Adjunctive Dexamethasone in Listeria Meningitis

45

- French nationwide prospective cohort study of 252 patients with neurolisteriosis, 13% of whom received dexamethasone (Lancet Infect Dis 2017;17:510)
  - Increased mortality in those receiving dexamethasone (48% vs. 27%)
- Dutch prospective cohort study of 162 patients with Listeria meningitis, 58% of whom received dexamethasone (eClinicalMedicine 2023;58:101922)
  - Rate of unfavorable outcome higher in those not receiving dexamethasone (72% vs. 46%)
  - Not receiving dexamethasone was associated with an increased risk of death in the multivariable analysis (OR 0.40; CI 0.19-0.84)

45

46

QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

46

Tuesday, August 19, 2025

44

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

Rajesh Gandhi, MD

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

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

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

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.

3

Question #1

50-year-old 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

4

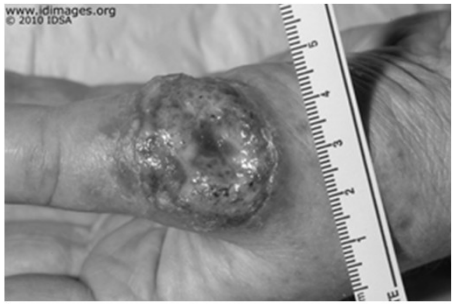
Question #1

PE: Patient appeared well; Temp 98.1

Raised ulcerated lesion on thumb with a violaceous border

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

Differential Diagnosis



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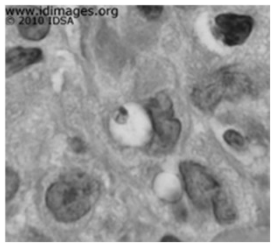
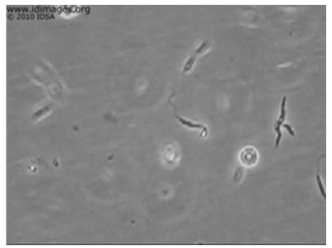
Skin biopsy showed amastigote, with kinetoplast in a vacuole. Culture of tissue from skin biopsy in Schneider's Media revealed promastigotes.

PCR of tissue: *Leishmania guyanensis*



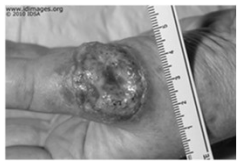
Skin biopsy, H and E stain



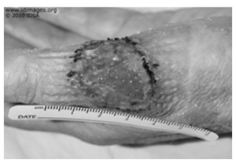
Culture of skin biopsy tissue in Schneider's medium

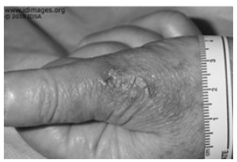
6

Treated with Liposomal Amphotericin



One week after treatment





Follow-up at 3 months

7

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

8

Question #2

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

9

Question #2

Labs: WBC 12,000 (neutrophils 43%, bands 38%, lymphocytes 10%). Creatinine 1.8

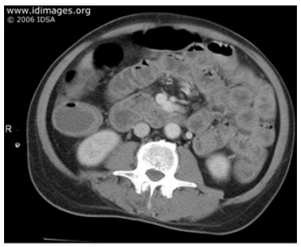
Clinical course:

- Patient received iv fluids because of concern for acute gastroenteritis and dehydration
- On hospital day 3, developed lethargy and fever (temp 102.4)
- Shortly thereafter, developed respiratory failure and Klebsiella was isolated from blood cultures (4/4 bottles) and cerebrospinal fluid

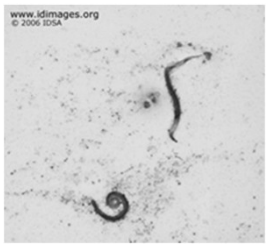
10

Question #2

Abdominal CT:
colonic wall inflammation



Gram stain of sputum



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

11

Strongyloides Hyperinfection Ayndrome

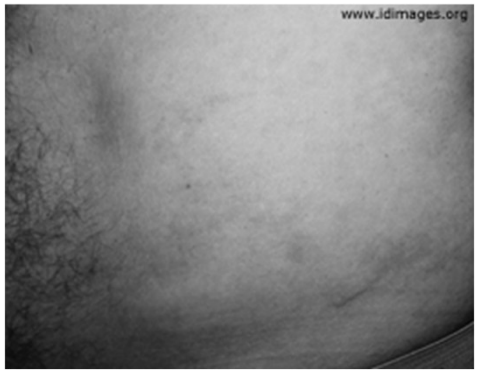
- May occur during immunosuppression, even short courses of steroids
- Accelerated autoinfection
- Larval migration in GI tract, lungs, skin and, at times, other organs
- Migration of filariform larva may be associated with entry of enteric bacteria (eg, gram-negative sepsis, meningitis)
- Peripheral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

Iodine stain of stool showed Strongyloides

12

Larva currens: Cutaneous Strongyloidiasis

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



13

Question #3

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

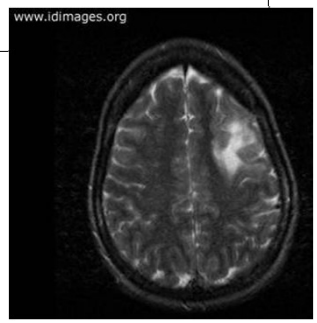
Contributed by Wendy Yeh, M.D.

14

Question #3

What is the most likely diagnosis?

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

15

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

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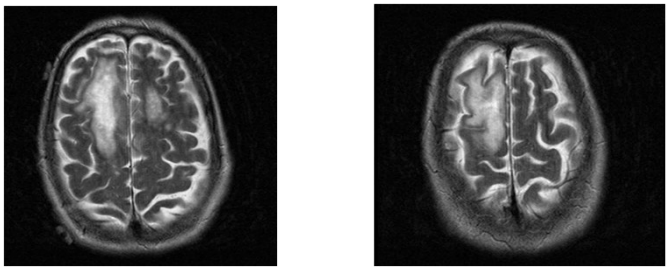
PML



Contributed by Vince Marconi, M.D.

17

Differential Diagnosis

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

18

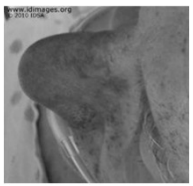
Question #4

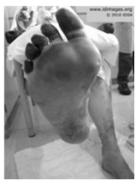
60-year-old M was well until day of admission when he developed lethargy and confusion. Over the course of the day, his hands and feet grew cold and numb, and he developed a rash.

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

19

Question #4





PE: Temp 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

20

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)

21

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

22

Question #5

- Woman in her 40s with multiple sclerosis presented with several months of joint pain and swelling
- Subsequently developed confusion; hospitalized for evaluation

Past medical history

- Hypogammaglobulinemia
- Intrauterine device complicated by peritoneal abscess several years prior to admission; cultures unrevealing
- Medications: prednisone 5 mg daily; rituximab

Epidemiologic history

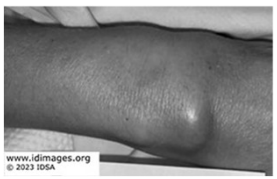
- Lived in Southern US. No travel outside US. Animals: cat. One male partner

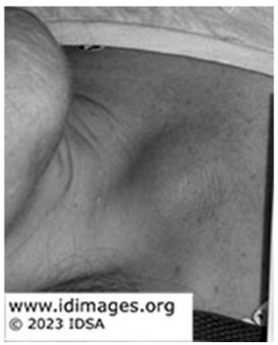
23

Question #5

Physical exam

- Afebrile
- Nodule over wrist
- Swelling, right sternoclavicular joint





Labs

- WBC 13.8
- CRP 266
- Serum ammonia 97 (elevated)
- Arthrocentesis: 194,000 nucleated cells (87% polys). Gram stain negative

24

Question #5

What is the diagnosis?

A. *Histoplasma capsulatum*

B. *Ureaplasma urealyticum*

C. Gonococcal infection

D. Chronic Recurrent Multifocal Osteomyelitis (CRMO)

E. *Borrelia burgdorferi*

25

Diagnostic Procedure and Result:

- Synovial fluid aspirate of wrist: *Ureaplasma urealyticum* by 16S PCR analysis.

26

Ureaplasma urealyticum

- Mycoplasmataceae family, along with Mycoplasma species
- Usually associated with genitourinary infections
- May cause infectious arthritis in people with immunocompromising conditions, such as hypogammaglobulinemia
- Disseminated *Ureaplasma* may mimic rheumatoid arthritis, including nodules
- Hyperammonemia due to IgA protease production by Ureaplasma.

27

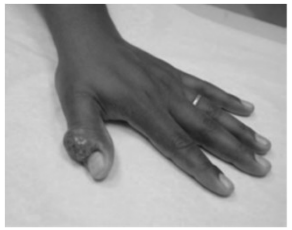
Question #6

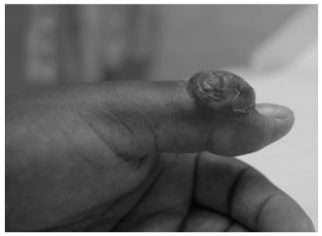
- 35-year-old man of Ethiopian descent cut his left thumb with a knife while slaughtering a lamb as part of Easter festivities. He washed the wound with water and applied lemon juice and alcohol. One week later, he developed swelling and tenderness and a fluctuant lesion at the site.
- Two weeks after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

28

Question #6

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

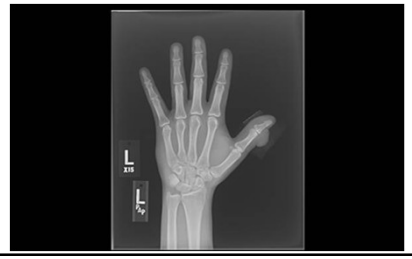




29

Question #6

- Creatinine and LFTs normal. Glucose 158. WBC 4.2 (normal differential)
- X-ray: fungating soft tissue lesion on dorsal aspect of distal thumb; no underlying bone or joint abnormality

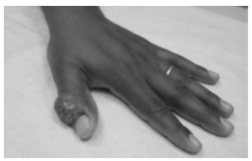


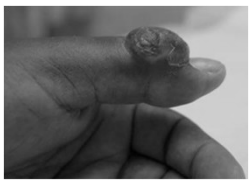
30

Question #6

What is the diagnosis?

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



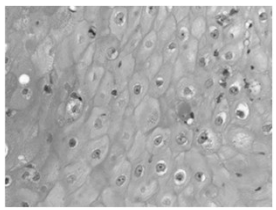


Contributors: Drs. Isaac Bogoch, Rajesh Gandhi

31

Follow-up

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



Appearance consistent with ecythma contagiousum

32

Orf (Contagious Ecthyma)

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

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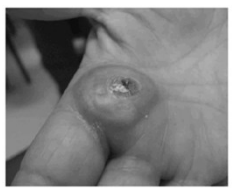
Orf (Cont.)

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

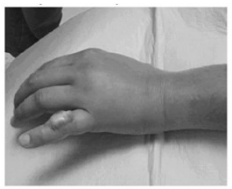
34

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

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



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



35

Question #7

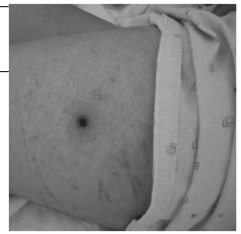
- 50-year-old F was well until 7 days prior to admission when she noted “bite” on left thigh. Lesion enlarged over several days. Four days prior to admission, developed fatigue, arthralgias, myalgias, fever, headache. On admission (July), developed generalized rash on extremities, trunk, back.
- **SH:**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

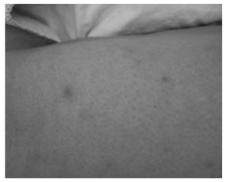
36

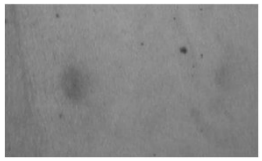
Question #7

What does this patient most likely have?

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







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Rickettsialpox

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

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Rickettsialpox vs. Chickenpox

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

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

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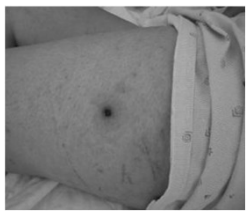
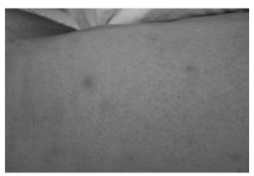
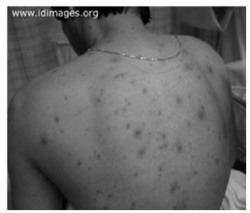
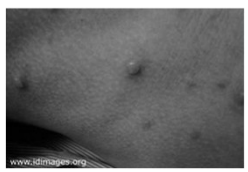
Rickettsialpox





Chickenpox





40

Question #8

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

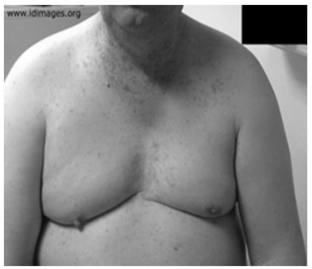
Contributed by Drs. Jessica Haberer, Justin Chan, Rochelle Walensky

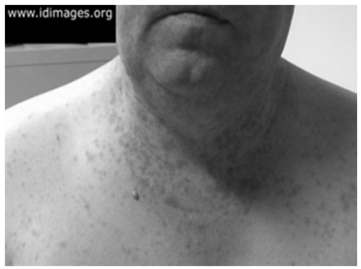
41

Question #8

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

WBC 3.3. Platelets normal.





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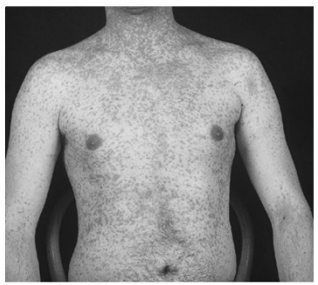
Question #8

Rash in a different patient with same infection

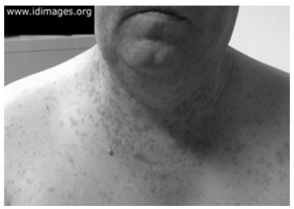


43

Question #8

Differential Diagnosis

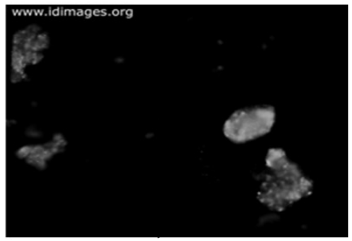
A. Syphilis
B. Scarlet fever
C. Parvovirus infection
D. Measles
E. Rocky mountain spotted fever



44

Measles

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



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

45

Measles

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

46

Question #9

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

Epidemiologic history

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

47

Question #9

Physical Examination

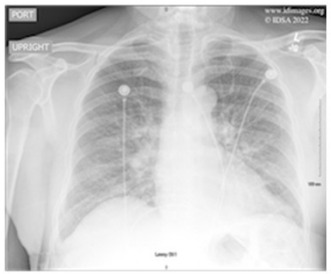
- Mild respiratory distress
- BP 141/80. Pulse 94. Temp. 97.7 ºF, RR 20, oxygen sat 93% on 6 L oxygen by nasal canula
- Respiratory exam: rhonchi at the lung bases
- Examination was otherwise normal

Studies

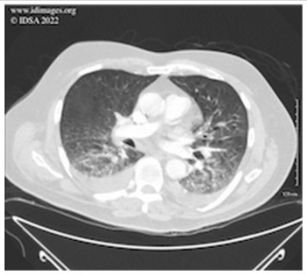
- WBC 19.3; 10% atypical lymphocytes; no eosinophilia
- Hemoglobin 18.4 g/dL. Hematocrit 52.6%. Platelets 102,000
- Chlamydia pneumoniae, Mycoplasma, HIV-1/2, Coxiella serologies were negative
- *Legionella pneumophila* urine antigen were negative
- Respiratory viral panel negative

48

Question #9 (Studies)



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



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

49

Question #9

Clinical Course Prior to Diagnosis

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

50

Question #9

What is the diagnosis?

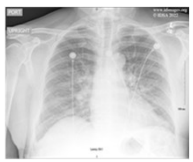
A. Coccidioidomycosis

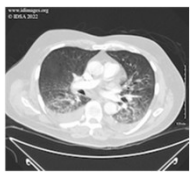
B. Legionella pneumonia

C. Hantavirus Cardiopulmonary Syndrome

D. Leptospirosis Pulmonary Hemorrhage Syndrome

E. Tularemia





51

Follow-up

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

52

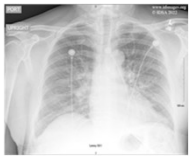
Hantavirus Cardiopulmonary Syndrome (HCPS): Clues

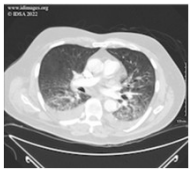
- Most cases are in southwestern US; first recognized in Four Corners region
- Transmitted by rodent reservoir, often in rural settings
- Febrile illness, bilateral interstitial infiltrates, and respiratory compromise requiring oxygen within 72 hours of hospitalization
- Cardiopulmonary phase characterized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

53

Final Diagnosis

- Hantavirus Cardiopulmonary Syndrome (HCPS)





Contributed by Dr. Dave Patel

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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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Tuesday, August 19, 2025

45

Herpes Simplex

Richard Whitley, MD

Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

Richard J. Whitley, MD

Co-Director, Division of Pediatric Infectious Diseases

Loeb Eminent Scholar Chair in Pediatrics
Professor of Pediatrics, Microbiology, Medicine, and Neurosurgery
The University of Alabama at Birmingham

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- Steering Committee: NIAID COVID-19 Recover Study, NIAID Recover VITAL Study
- Scientific Advisory Board: Treovir, LLC
- Scientific Advisory Board: Altesa Biosciences
- Member, Board of Directors at Evrys Bio
- Member, Board of Directors at Virios Therapeutics
- Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB

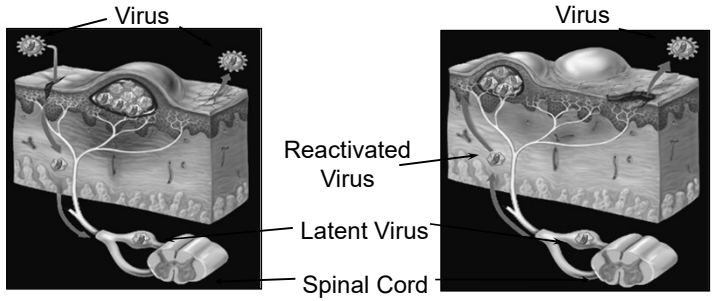
2

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)

3

Viral Latency and Reactivation

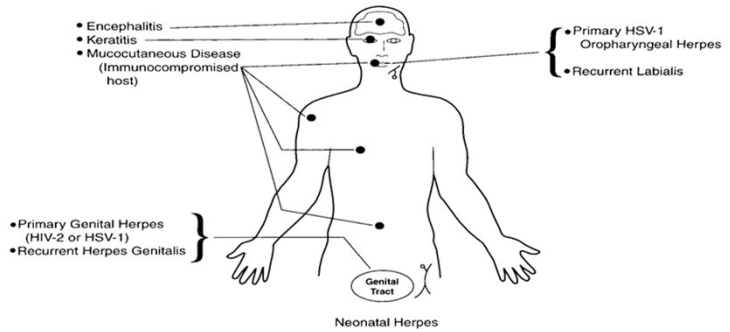


Netter FH. ©2001 by Icon Learning Systems.

4

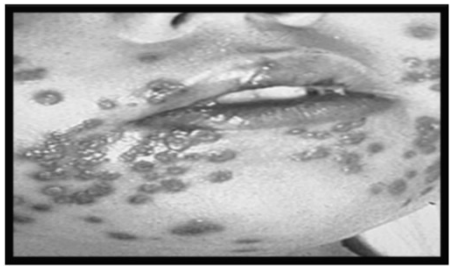
45 Herpes Simplex
Speaker: Richard Whitley, MD

Clinical Manifestations of Herpes Simplex Virus Infections



5

Primary Herpes Simplex Virus Infection: Cutaneous Lesions



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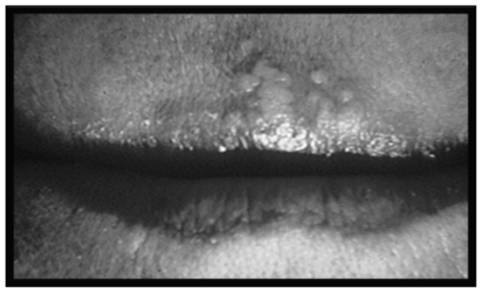
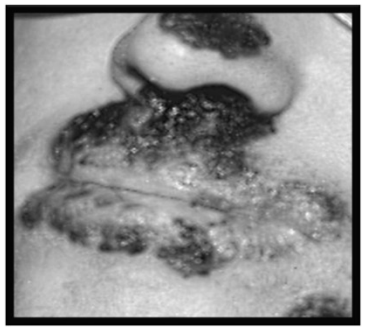
Herpes Simplex Labialis



7

Immunocompromised Host



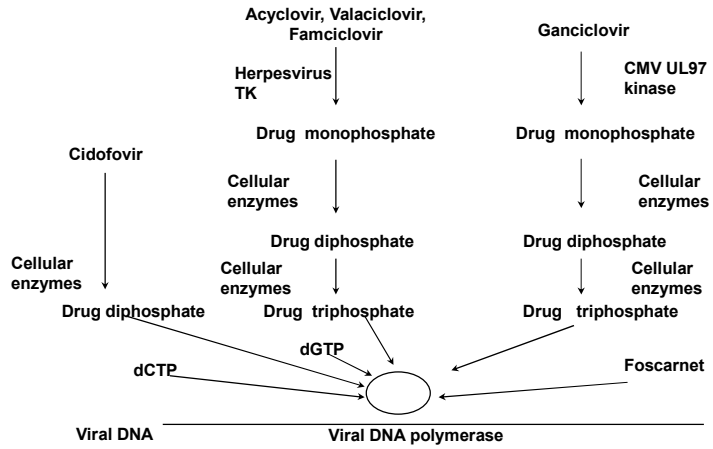
8

45 Herpes Simplex
Speaker: Richard Whitley, MD

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

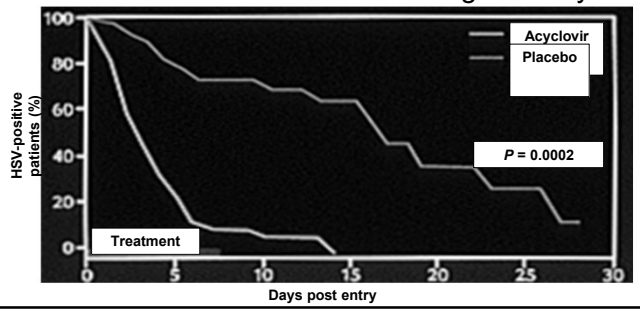
9



10

Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

Time to cessation of viral shedding with acyclovir



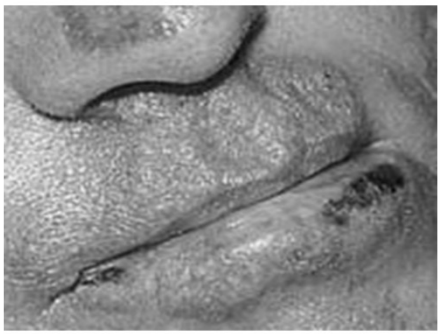
11

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	

12



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Question #1

PREVIEW QUESTION

INFECTIOUS DISEASE BOARD REVIEW 2025

A 30-year-old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive despite high-dose intravenous therapy.

Instead of healing, as shown a previous slide, the lesions progress despite antiviral therapy.

A deficiency or alteration of which of the following is the most likely cause for disease progression?

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

14

Question #2

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

15

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)

16

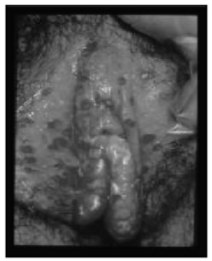
Acyclovir Therapy of Genital Herpes

Summary of clinical benefit for treatment of:

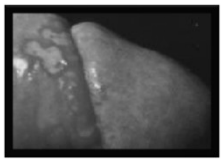
- Primary
- Recurrent
- Suppressive

17

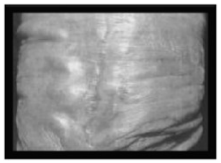
Spectrum of HSV Clinical Presentation



First infection



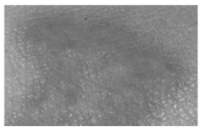
Classical recurrence



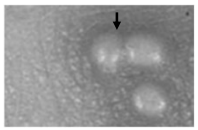
Atypical recurrence

18

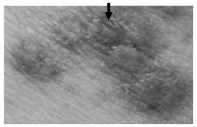
Progression of Lesions



Early Redness/Swelling



Thin-Walled Fluid-Filled Vesicles and Pustules

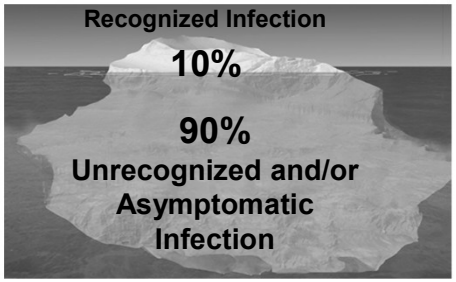


Early Healing of Vesicles, Erosions, or Ulcers

19

Clinical Spectrum of HSV-2

HSV-2 Seroprevalence



Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839.

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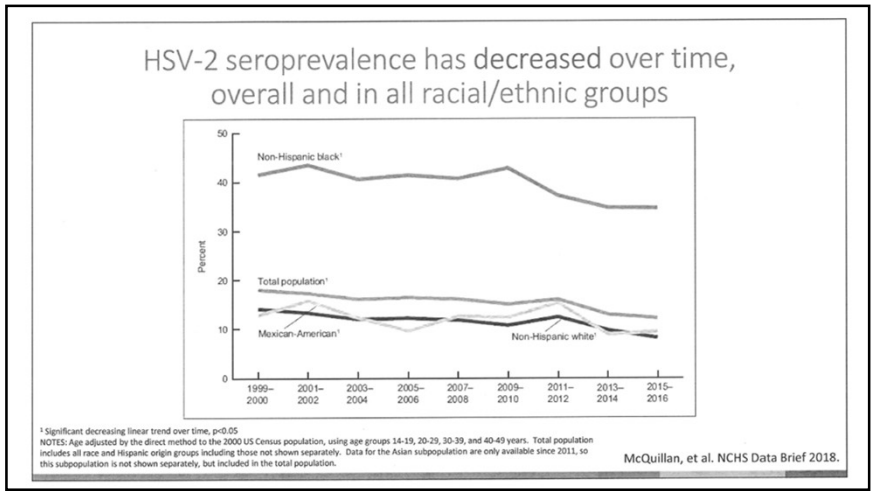

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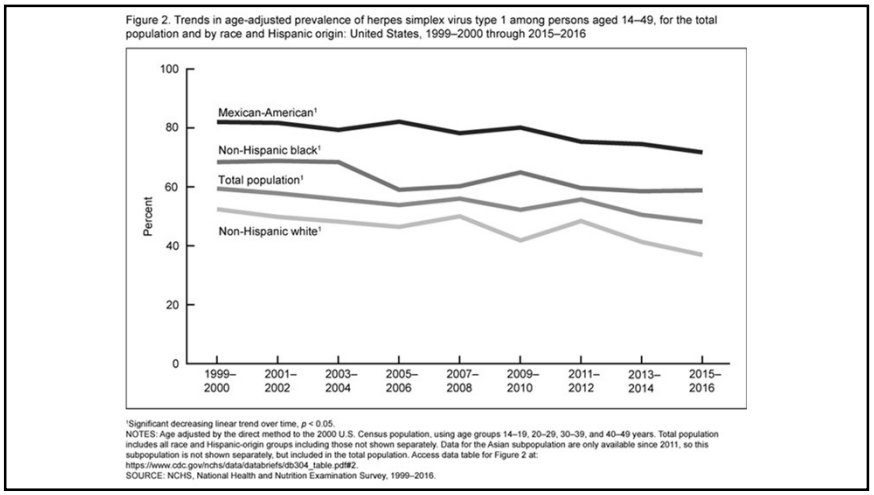

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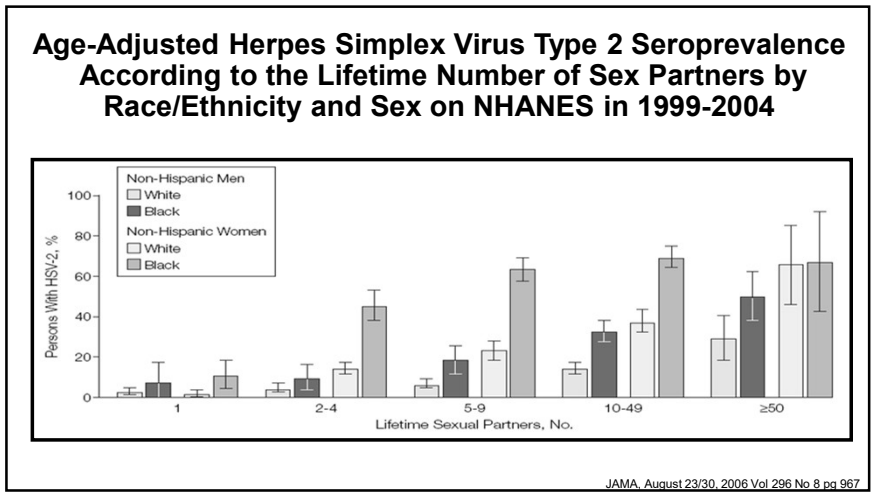

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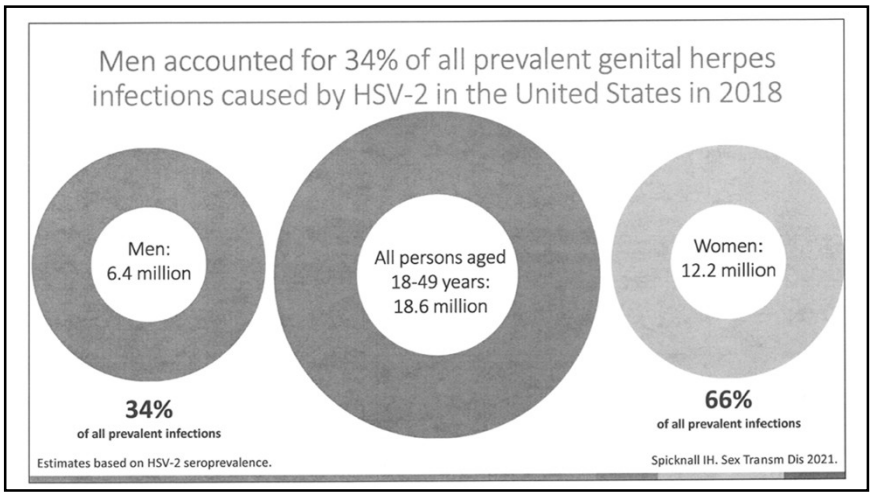

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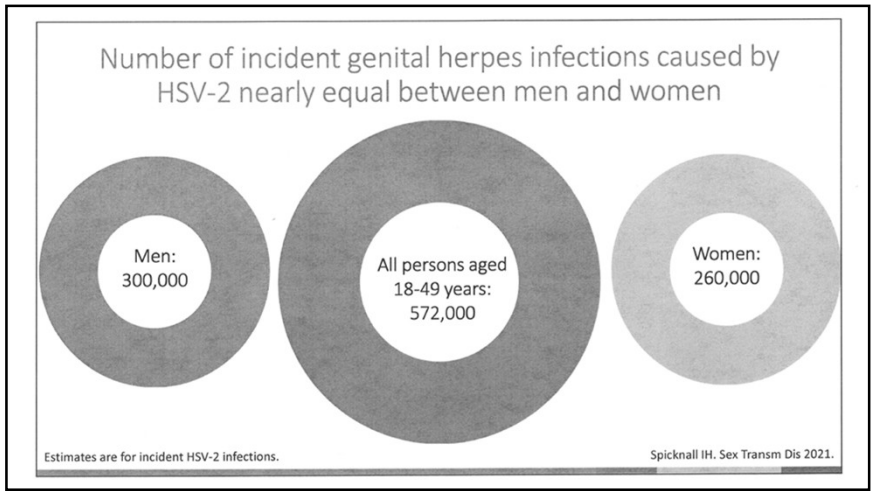


25

Genital Herpes: Transmission

Men — Asymptomatic Recurrence ⇄ Women

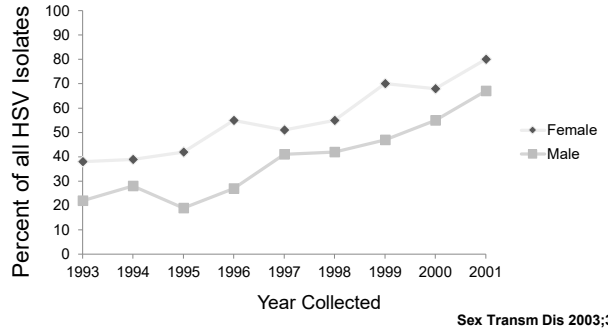
Transmission — Symptomatic Recurrence → 30%

Transmission → 70%

Corey L. *Sex Transm Dis.* 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.

26

HSV-1 Genital Isolates Among U.S. College Students

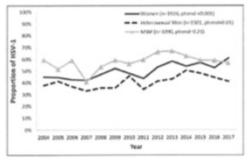


Sex Transm Dis 2003;30:797-800

27

Changing epidemiology of first episode genital herpes

Melbourne Sexual Health Center



In 2017, 54% of first episode genital herpes was due to HSV-1

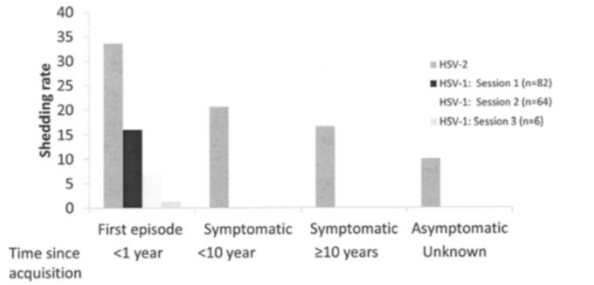
Public Health-Seattle & King County

Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

28

Genital Shedding Rate: HSV-2 vs. HSV-1



Johnston et al, ISSTDR 2019
Phipps *et al*, JID 2011
Tronstein *et al*, JAMA 2011

29

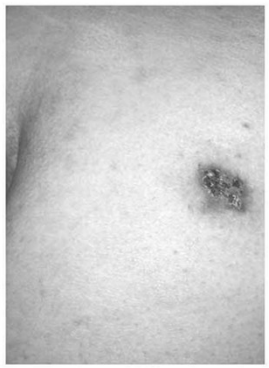
Genital Herpes: Viral Shedding

- 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.

30

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.

31

Question #3

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

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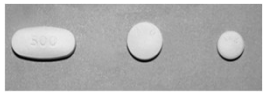
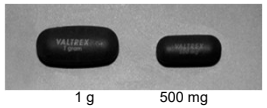
Oral Antiviral Therapies

- **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.

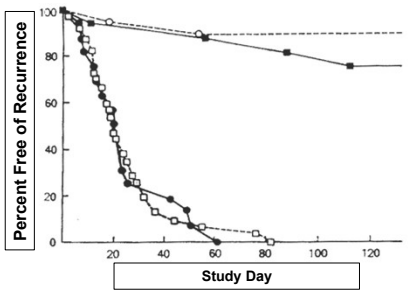
33

Impact of Acyclovir Therapy on Primary Genital HSV Infection

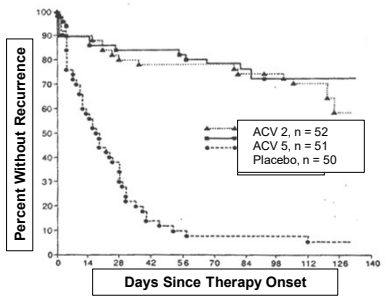
	Treatment Group (Days)			
	Acyclovir	**Placebo**	**RR**	**P**
Virus Shedding	**2.8**	**16.8**	**6.82**	**0.0002**
Pain	**8.9**	**13.1**	**2.00**	**0.01**
Scabbing	**9.3**	**13.5**	**2.21**	**0.004**
Healing	**13.7**	**20.1**	**1.83**	**0.04**

34

Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes



Straus, et al. *NEJM*, 1984



Douglas, et al, *NEJM*, 1984

35

Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

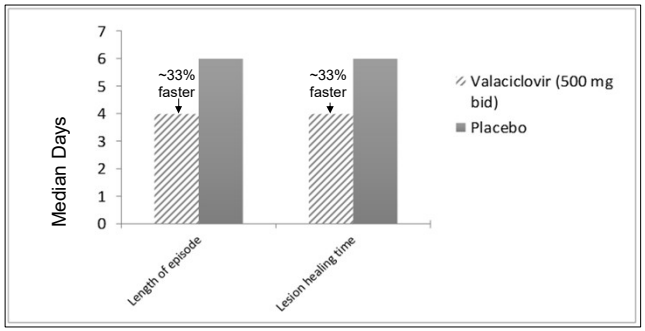
36

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

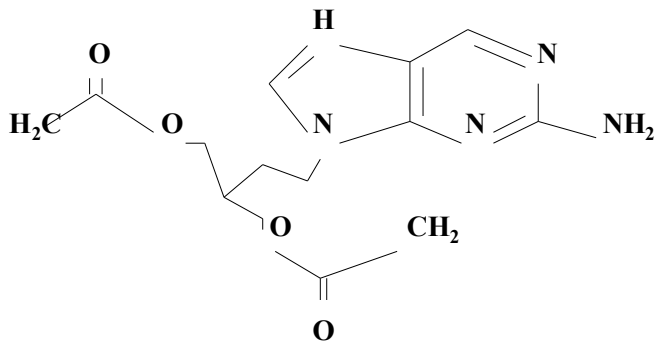
37

Therapy of Recurrent Genital Herpes: Duration of Disease



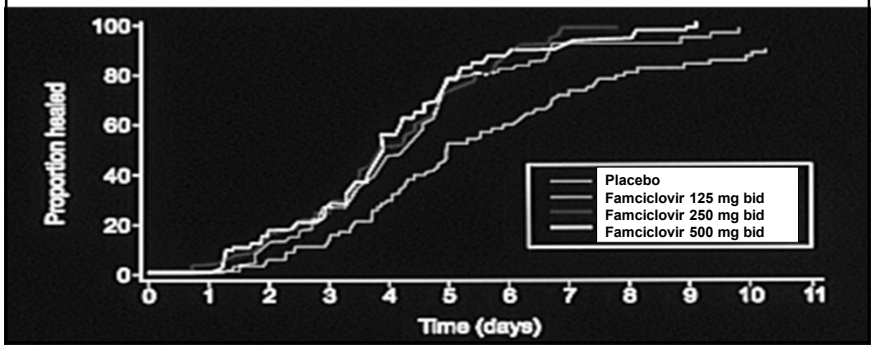
38

Famciclovir



39

Famciclovir Therapy of Recurrent Genital Herpes



40

45 Herpes Simplex

Speaker: Richard Whitley, MD

Shorter and Shorter Therapy

- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

41

Prevention of Person-to-Person Transmission

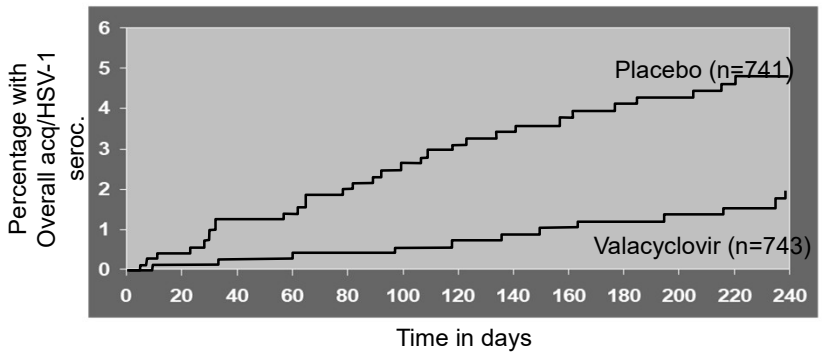
42

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

43

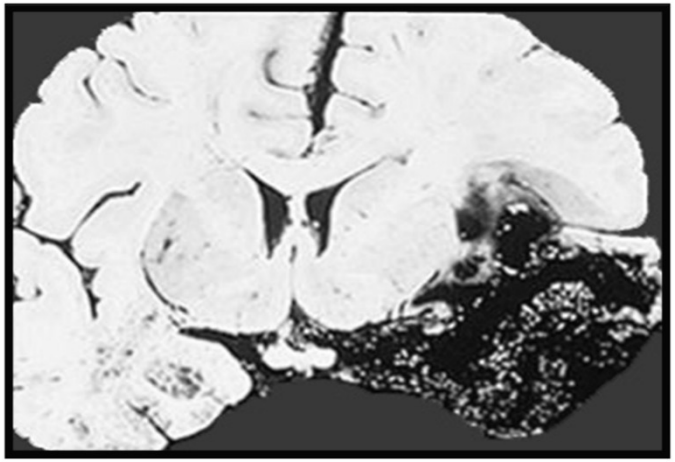
Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners



44

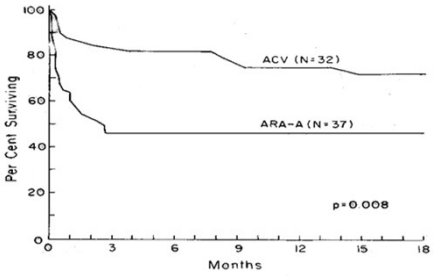
45 Herpes Simplex

Speaker: Richard Whitley, MD



45

Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A)
vs
Acyclovir (ACV);
P=0.008

46

HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

47

Sensitivity and Specificity of PCR

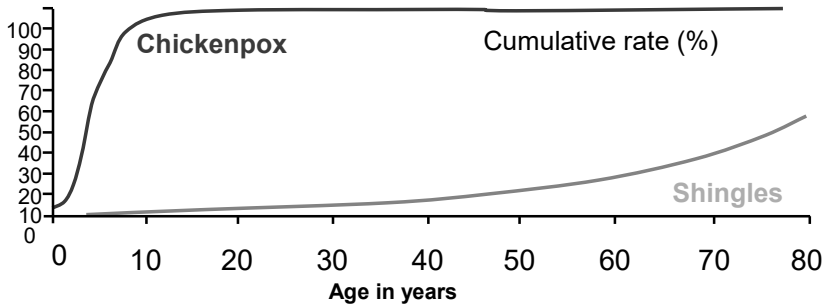
	Biopsy Positive	Biopsy Negative
PCR Positive	53	3
PCR Negative	1	44

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

48

45 Herpes Simplex
Speaker: Richard Whitley, MD

Varicella Zoster Virus Infection



Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

49

CHICKEN POX: Is Therapy of Value?

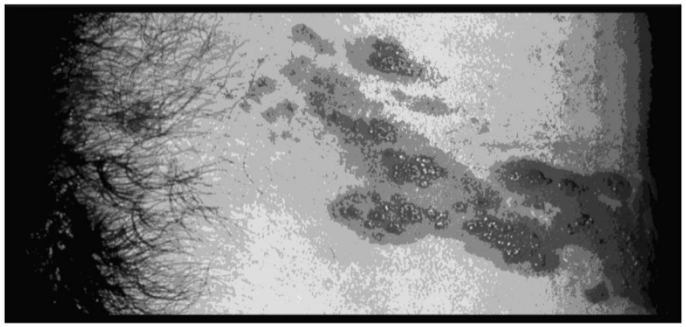
50

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

51

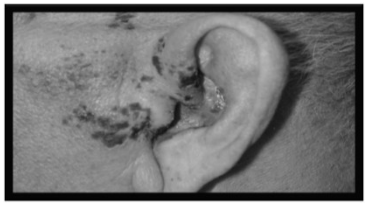
Thoracic Herpes Zoster



52

Questions

1. What is the most likely diagnosis?
2. How would you prove the etiology?



53

Answer

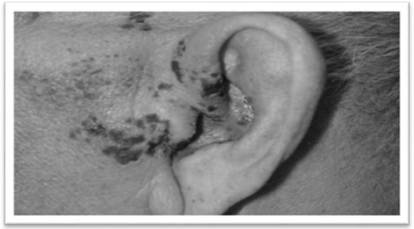
- Clinically this is herpes zoster
- The lesion shown is Tzank prep positive on skin scraping. The sensitivity of this test is only ~60% and, therefore, is not recommended
- Immunofluorescence is positive for VZV, having a sensitivity of ~80%
- Preferably, PCR can be performed even when lesions are scabbed and has the highest sensitivity

54

Question #4

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

55

Question #4

- This patient has Ramsay Hunt syndrome (Herpes zoster oticus), caused by VZV reactivation in the geniculate ganglion, i.e. zoster of CN VII, presenting with severe ear pain and reduced hearing or deafness. When vesicle are seen in the auditory canal, abnormalities in cranial nerves VII, and sometimes VIII, IX or X, can occur. Thus A, facial paralysis is the best answer. Acyclovir is usually recommended although its not clear if it's effective. The facial paralysis is more severe and less likely to resolve than the usual HSV related Bells Palsy.
- Keratitis would be more typical of a lesion on the tip of the nose, or zoster ophthalmicus involving the CN V ophthalmic branch.
- Encephalitis can be caused rarely by VZV and would not be the best answer. Stroke syndromes due to carotid intimal involvement are associated with zoster, and often with cranial nerve V (trigeminal involvement), but are not offered as an answer
- Optic neuritis and oculomotor paralysis would be uncommon.

56

Question #5

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

57

Question #5

What complication is most likely to be associated with this illness?

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

www.medscape.com

58

Question #5

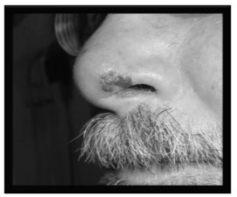
This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e., ophthalmic branch of the trigeminal nerve, which innervates the tip of the nose and the globe. After a prodrome of fever and headache for 1-4 days, patients develop a cutaneous rash. Days or up to 3 weeks later, the sclera and cornea can be involved. Thus, keratitis is the correct answer.

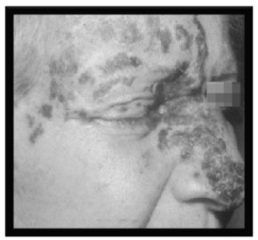
Deafness or vertigo would be more characteristic of geniculate ganglion (CN VII) involvement, i.e., Ramsay Hunt, which is a polyneuropathy involving the cranial nerve VII, and then often involves VIII, IX, X. Thus, A and B are not the best answers.

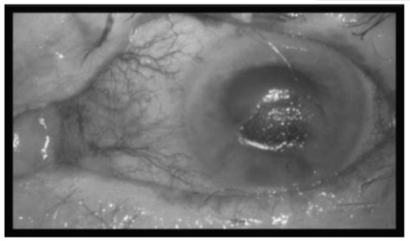
59

Hutchison's Sign

Zoster Involving nasociliary branch, Cranial Nerve VII which innervates the tip of the nose and the cornea

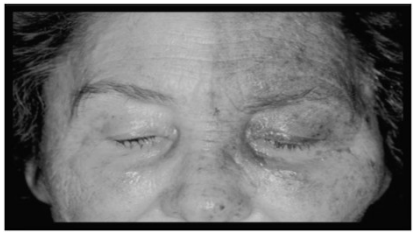






60

Zoster Ophthalmicus



61

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

62

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

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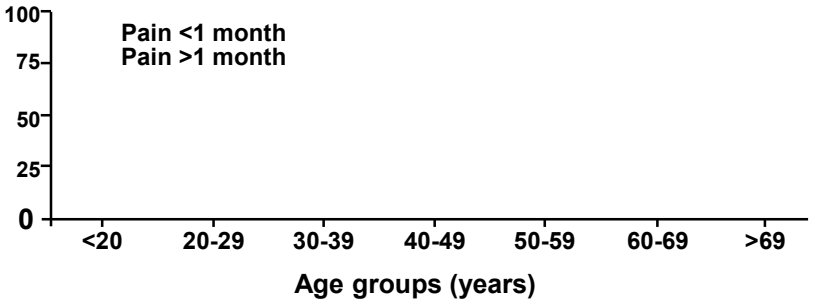
Complications of Zoster

Common	Uncommon
• Postherpetic neuralgia	• Cutaneous dissemination
• Ocular complications	• Herpes gangrenosum
• Ophthalmic zoster	• Hepatitis
• (Uveitis, keratitis, scleritis, optic neuritis)	• Encephalitis
• Pneumonitis	• Motor neuropathies
• Scarring	• Myelitis
• Bacterial superinfection	• Hemiparesis (granulomatous CNS vasculitis)

64

Prevalence and Duration of Pain



de Moragas et al. *Arch Derm.* 1957;75:193-196.

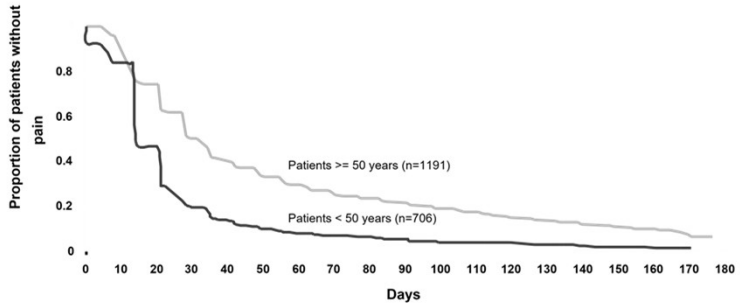
65

Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

66

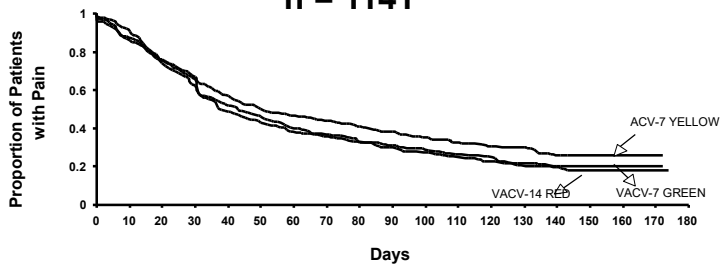
Time to Cessation of Zoster-Associated Pain



67

Time to Cessation of Zoster-Associated Pain

n = 1141



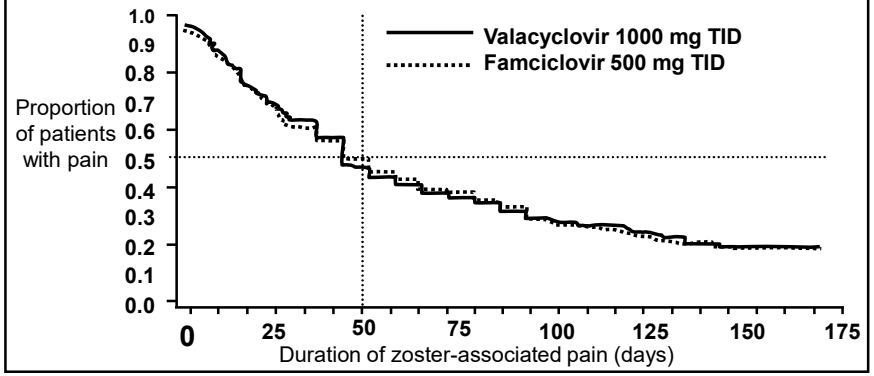
* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

68

45 Herpes Simplex

Speaker: Richard Whitley, MD

Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



69

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

70

Question #6

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6

www.cdc.gov

71

Question #6

- This patient has facial palsy, also known as Bells palsy. The most likely cause of this lesion is HSV. HIV and Lyme disease are less common causes. Answers d and e are not the best answer. Of note, Lyme is rarely the cause of Bells palsy unless there are other manifestations of Lyme disease.
- For typical facial palsy, prednisone is the preferred therapy, optimally given within 3 days of onset, for one week (prednisone 60-80mg qd). Acyclovir alone is not better than placebo, although there might be some rational (unproven) to add acyclovir to prednisone.
- Ganciclovir would be a therapy for CMV, a rare cause of facial paralysis and thus not the best answer.

72

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)

73

Second Generation Vaccine: Shingrix

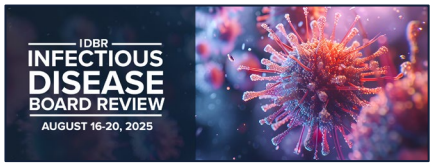
- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

75

Thank You

rwhitley@uabmc.edu

76



Agenda Day 5: Wednesday, August 20, 2025

#	Start		End	Presentation	Faculty
AM Moderator: John Bennett, MD					
46	8:00 AM EDT	-	9:00 AM EDT	Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices	Henry Chambers, MD
47	9:00 AM	-	9:45 AM	Encephalitis including West Nile and Rabies	Allan Tunkel, MD
	9:45 AM	-	10:00 AM	Morning Break	
48	10:00 AM	-	10:45 AM	Staphylococcus aureus	Henry Chambers, MD
49	10:45 AM	-	11:30 AM	Bone and Joint Infections	Sandra Nelson, MD
	11:30 AM	-	11:45 AM	Lunch Break	
PM Moderator: Barbara Alexander, MD					
50	11:45 AM	-	12:30 PM	Nontuberculous Mycobacteria in Normal and Abnormal Hosts	Kevin Winthrop, MD
51	12:30 PM	-	1:30 PM	Infections in Solid Organ Recipients	Barbara Alexander, MD
	1:30 PM	-	1:45 PM	Afternoon Break	
52	1:45 PM	-	2:30 PM	Core Concepts: Antifungal Drugs	Barbara Alexander, MD
53	2:30 PM	-	2:45 PM	Penicillin Allergies	Sandra Nelson, MD
54	2:45 PM	-	3:30 PM	Kitchen Sink: Syndromes Not Covered Elsewhere	Stacey Rose, MD

Wednesday, August 20, 2025

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

Henry Chambers, MD

Endocarditis of Native and Prosthetic Valves, Infections of Cardiac Implantable Devices

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

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- Merck – Stock and DSMB member
- Moderna - Stock

2

Topics for Discussion

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

3

Diagnosis of Endocarditis

4

46 Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices
Henry Chambers, MD

Question #1

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

5

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

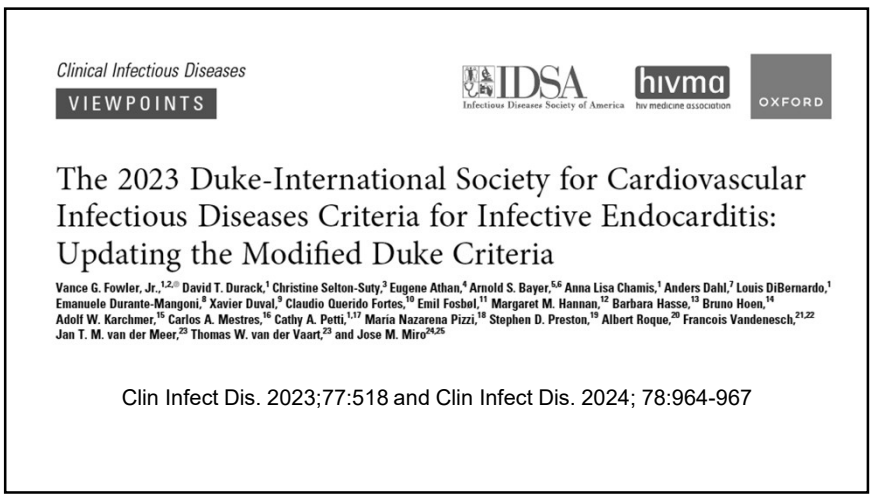
6

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

7



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

8

Weaknesses of "Old" Modified Duke Criteria

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

9

2023 Duke-ISCVID Criteria for Diagnosis of Endocarditis

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

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

10

2023 Duke-ISCVID Major Criteria

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

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

11

2023 Duke-ISCVID Minor Criteria

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

12

What about "Possible" IE Cases?

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

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

13

Performance of New vs Old Duke Criteria

Sensitivity

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

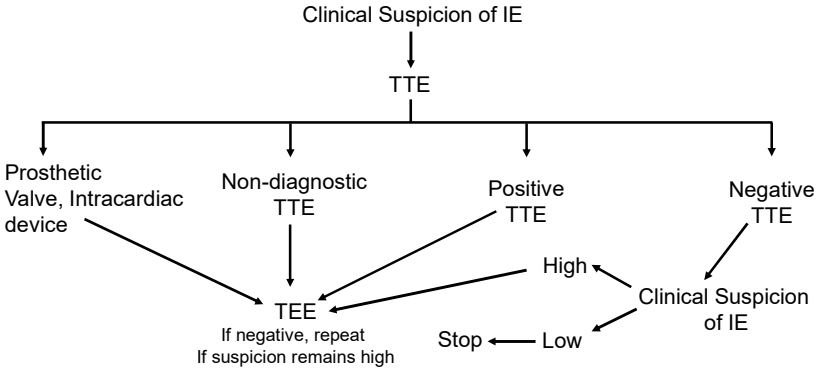
Specificity

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

Chambers, et al. Duke Infective Endocarditis Criteria 3.0 for the Clinician: Defining What Is Possible. Clin Infect Dis. 2024, 78:964

14

Role of Echocardiography



European Heart Journal (2015) 36, 3075–3123

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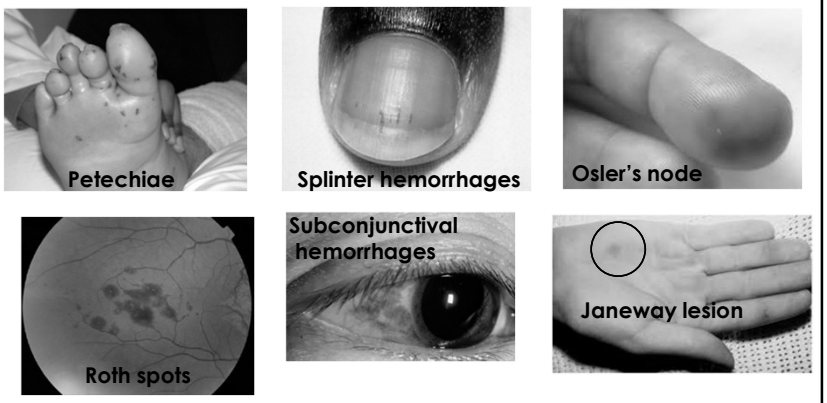
Microvascular/Immunologic Phenomena



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

Henry Chambers, MD

Native Valve Endocarditis

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Question #2

A 63-year-old 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.

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Question #2

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

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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
MRSA		
Vancomycin	6 wk	For MSSA if a beta-lactam cannot be used
Daptomycin	6 wk	10 mg/kg/day, vanco alternative

No gentamicin, no rifampin

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Question #3

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

Exam: BP 135/90 P100 , 38.2°C
- 3/6 holosystolic murmur, radiating the the axilla
- Lungs are clear, no peripheral stigmata of endocarditis

- Serum creatinine 1.2 mg/dl
- TTE: mitral valve prolapse with 0.5 cm vegetation on anterior leaflet, moderate regurgitation
- 3/3 blood cultures from admission positive for *Streptococcus mitis*, penicillin MIC = 0.25 μg/ml, ceftriaxone MIC = 0.25 μg/ml.

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Question #3

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

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Treatment of Viridans Group Strep and Strep. gallolyticus Native Valve Endocarditis

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

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Question #4

A 72-year-old 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: T 38.9°C, Pulse 110 , BP 145/95 mm Hg
  - Lungs are clear
  - 3/6 systolic ejection murmur at the right upper sternal boarder.
- Lab results
  - Serum glucose 340 mg/dl
  - Serum creatinine 1.7 mg/dl, BMP otherwise normal
  - UA: 3+ protein, 20-50 wbcs/high power field, 4+ glucose.
  - Two blood cultures and a urine culture are positive for ampicillin-susceptible *Enterococcus faecalis*.

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Question #4

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

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Enterococcal Endocarditis

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

*Limited data that 2 weeks of gent is sufficient

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HACEK Organisms

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

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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

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Empirical Therapy for Endocarditis While Awaiting Culture Results

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

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Oral Therapy of Endocarditis

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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

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POET Trial of Oral Therapy

- Noninferiority trial, 10% margin, left-sided endocarditis, IV vs partial oral
- Streptococci, Enterococcus faecalis, Staph. aureus (No MRSA), 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

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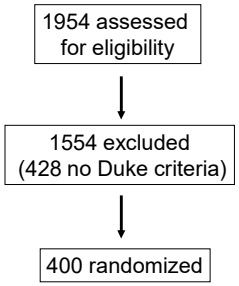
Outcomes: POET Trial of Oral Therapy



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

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Culture-Negative Endocarditis

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Question #5

A 37-year-old marginally housed male with a past history of injection drug use reports not feeling well for several weeks.

HPI: His reports intermittent fevers and thinks he has lost weight because clothes not longer fit him. He took a few doses of cephalexin given to him by a friend a couple of weeks ago which did not make much difference.

Exam: Tmax : 37.5°C/99.5°F; 2/6 systolic murmur on exam, otherwise WNL

Labs: CBC: mild normocytic anemia, hemoglobin 12 g/dL
UA: 50-100 red cells per high-power field
Serum creatinine: 3.6 mg/dL, high
C-reactive protein (CRP): 125 mg/L, high
C-ANCA (cytoplasmic antineutrophil antibody): positive
C3 complement: low
Blood cultures: negative at 96 hours

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Question #5

What is the most likely diagnosis in this patient not feeling well for several weeks?

1. Granulomatosis with polyangiitis
2. Culture-negative endocarditis due to Staphylococcus aureus
3. Culture-negative endocarditis due to a viridans group streptococcal species
4. Culture-negative endocarditis due to Bartonella hensalae
5. Culture-negative endocarditis due to Tropheryma whipplei

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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

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Culture-Negative Scenarios

- **Coxiella burnetii (Q fever)**: Direct or indirect animal contact, hepatosplenomegaly, abnormal or prosthetic valve. Doxycycline + hydroxychloroquine >1 yr.
- **Bartonella**: Homeless, indolent, valve normal or abnormal, louse vector. **Rx:** 6 wks doxycycline plus two wks gentamicin or plus 2 wks rifampin if valve resected (otherwise 3 months more of doxy)
- **Tropheryma whipplei:** 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, mNGS
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

mNGS = metagenomic next generation sequencing

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Prosthetic Valve and Device-Related Endocarditis

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Question #6

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

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

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Question #6

What is the best approach for managing this patient?

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

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Microbiology of PVE

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

Adapted from Karchmer and Chu, UpToDate, 2020

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Diagnosis of PVE

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

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

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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

Observations studies question role of gentamicin and even rifampin

45

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, Circulation 2024; 149:e201

46

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

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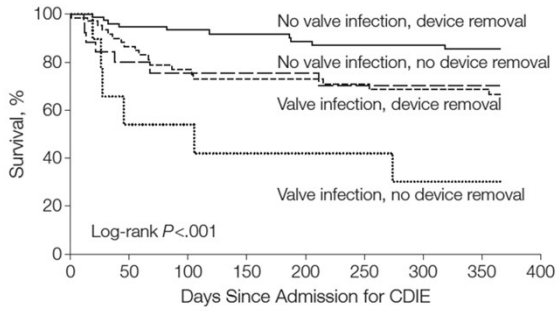
Survival with and without Device Removal



Athan, JAMA. 2012; 307:1727-1735

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

Henry Chambers, MD

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 ~~(consider 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

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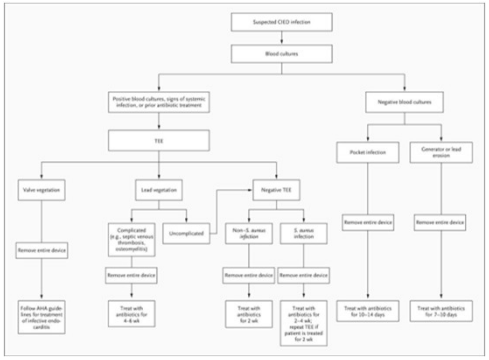
Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



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

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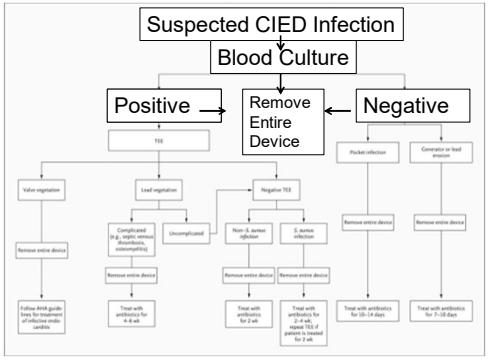
Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



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

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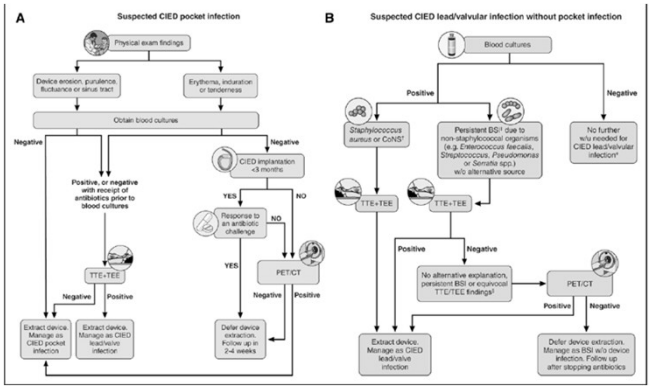
NEW Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



Circulation 2024; 149:e201

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

Henry Chambers, MD

Can Defer CIED Extraction 2-4 Weeks If

- Suspected pocket infection + negative blood cultures (before antibiotics) + implant < 3 mo + good response to oral antistaphylococcal antibiotic
- Suspected pocket infection + negative blood cultures (before antibiotics) + implant < 3 mo BUT response to antibiotics is suboptimal and PET/CT is negative

Circulation 2024; 149:e201

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Can Defer CIED Extraction If

- Suspected CIED infection but NO signs of pocket infection + ***negative blood cultures***
- Suspected CIED infection but NO signs of pocket infection + ***positive blood cultures*** + not S. aureus or CoNS, + clears in 72 hours if other organisms + alternative source
- Suspected CIED infection but NO signs of pocket infection + ***persistently positive blood cultures*** + no alternative source + TTE/TEE negative + PET/CT negative

Circulation 2024; 149:e201

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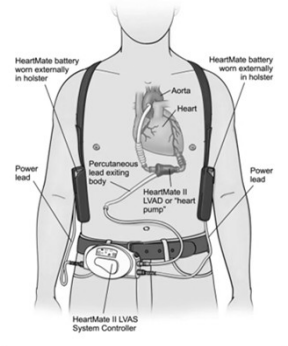
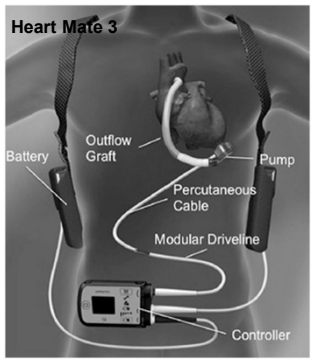
Infection of Ventricular Assist Devices





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Types of VAD Infections

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

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

56

Microbiology of VAD-Specific Infections

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

Clinical Transplantation 2019;33:e13552.

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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

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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

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IE Prophylaxis after Dental Procedures

YES

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

NO

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

Circulation. 2021;143:e963-e978

60

Which Dental Procedures?

YES

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

NO

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

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IE Prophylaxis Regimens

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

Single dose
30-60 min
before Procedure

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Main Take-home Points

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

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Other Stuff

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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

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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

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Fever During Therapy of Endocarditis

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

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Wednesday, August 20, 2025

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Encephalitis including West Nile and Rabies

Allan Tunkel, MD

Encephalitis Including West Nile and Rabies

Allan R. Tunkel, MD, PhD, MACP

Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Encephalitis
Definitions

3

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

3

Encephalitis
Epidemiology

4

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

4

Encephalitis
Etiology

5

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

5

Encephalitis
Etiology

6

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

6

Reasons Etiology not Identified

7

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

7

General Approach

8

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

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

8

Question #1

9

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

9

Question #1

10

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

10

Question #1

11

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

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

11

Question #1

12

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

12

Question #2

13

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

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

13

Herpes Simplex Encephalitis

14

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

14

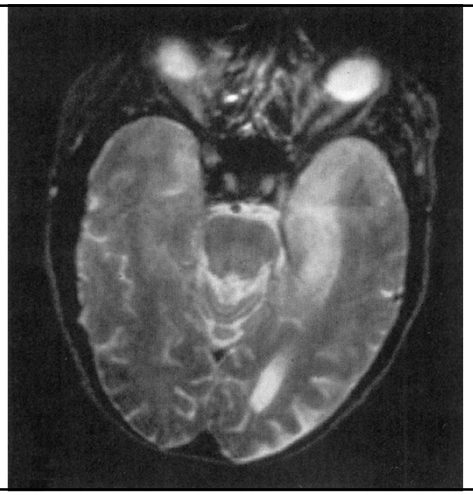
Herpes Simplex Encephalitis

15

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

15

18



16

Herpes Simplex Encephalitis

17

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

*Habis et al. Clin Infect Dis 2024;doi.org/10.1093/cid/ciae391

17

Herpes Simplex Encephalitis

18

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

18

Other Herpesviruses

19

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

19

Other Herpesviruses

20

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

20

Question #3

21

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

21

Question #3

22

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

22

Question #3

23

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

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

23

West Nile Virus (WNV) Encephalitis

24

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

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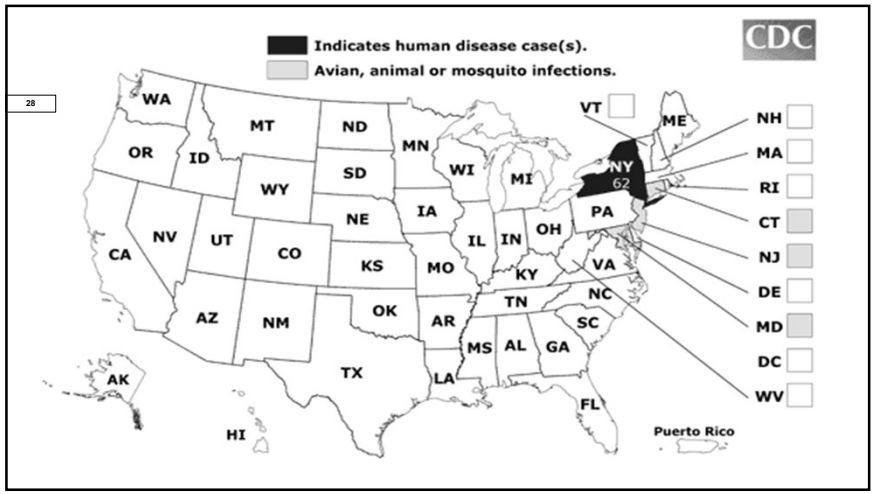

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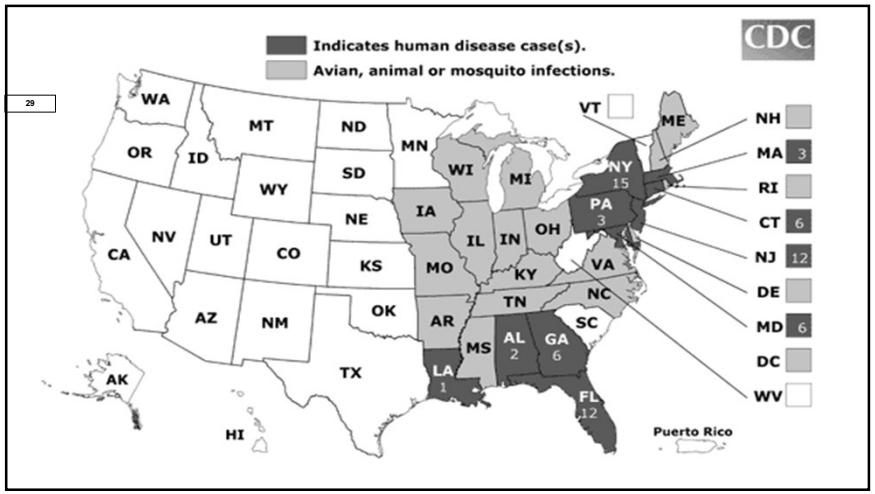

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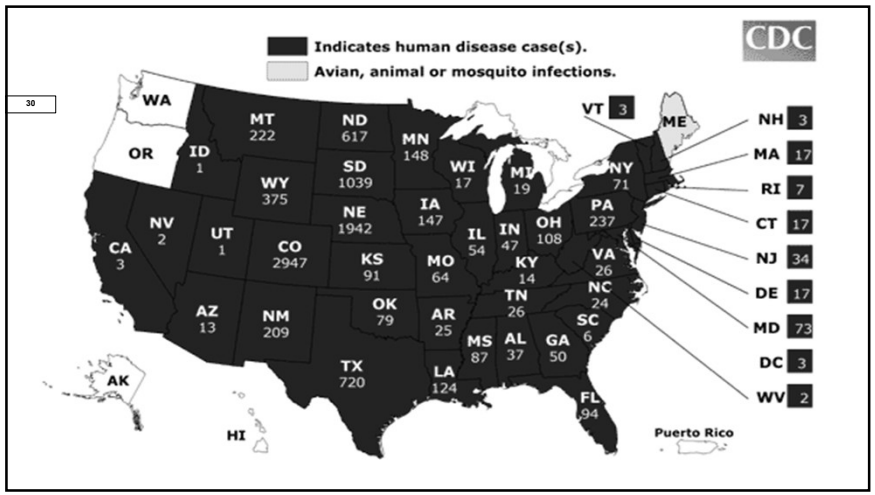

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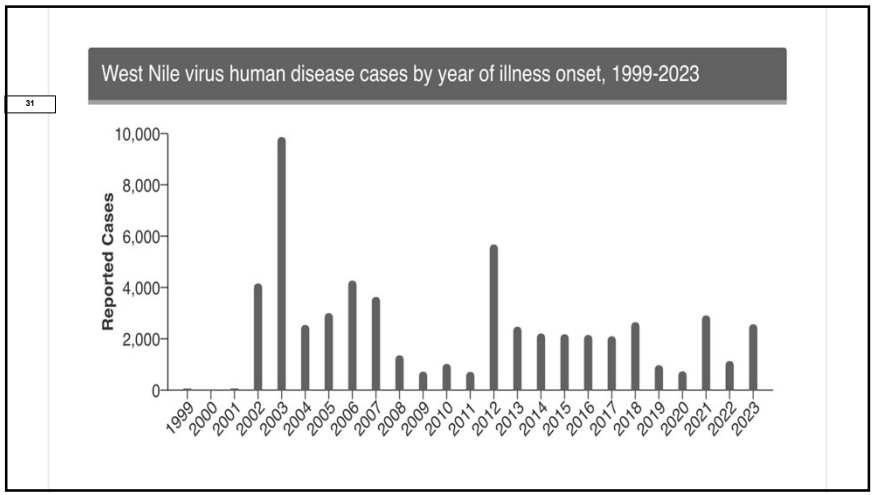

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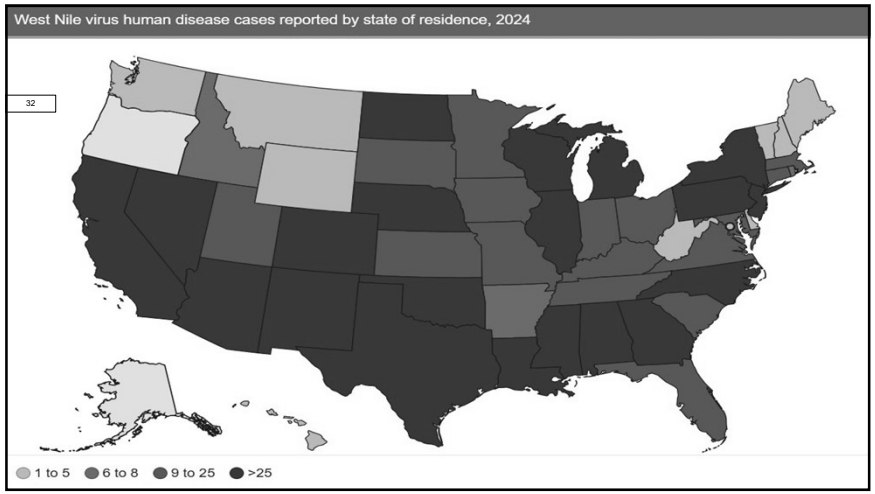
47 Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD, PhD, MACP



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West Nile Virus Clinical Syndromes

30

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

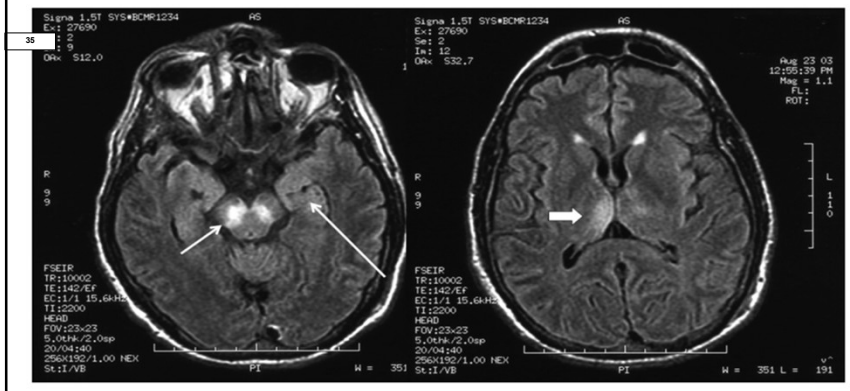
30

West Nile Virus Encephalitis

31

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

31



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47 Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD, PhD, MACP

West Nile Virus Encephalitis

33

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

33

Other Arboviruses

34

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

34

Other Arboviruses

35

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

35

Other Arboviruses

36

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

36

Measles Virus

37

- Primary encephalitis
  - Up to 1 per 1,000 infections
  - Usually appears within a few days (typically 5 days) of rash
  - Fever, headache, stiff neck, drowsiness, convulsions, coma
  - Rapidly progressive and fatal in ~15%
- Acute disseminated encephalomyelitis
  - Up to 1 per 1000 infections
  - Usually appears ~2 weeks after exposure
  - Demyelinating disease; post-infectious autoimmune response
  - Fever, fatigue, headache, nausea, vomiting
  - 10-20% mortality

37

Measles Virus

38

- Inclusion body encephalitis
  - Unvaccinated children and adults; immunocompromised
  - Symptoms 1-6 months after exposure;
  - Decreased consciousness, focal signs, seizures
- Subacute sclerosing panencephalitis
  - Acquisition of measles before 2 years of age
  - 6-10 years after infection (range 3-35 years)
  - Behavioral changes, cognitive impairment at presentation
  - Myoclonus, seizures, neurologic deterioration (coma and death) later

38

Meningitis/Encephalitis Panel

39

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

39

Metagenomic Next-generation Sequencing

- Allows unbiased or agnostic pan-species molecular diagnostics
- 204 patients (58 with meningitis or encephalitis), NGS identified an infectious cause in 22% not identified by clinical testing*
- 220 CNS infections, 40% identified by conventional methods and NGS, 22% by NGS alone and 36% only by conventional methods**
- Possible role in testing of enigmatic cases

*Wilson et al. NEJM 2019;380:2327

**Benoit et al. Nature Med 2024;30:3522

40

47 Encephalitis including West Nile and Rabies

Speaker: Allan Tunkel, MD, PhD, MACP

Question #4

41

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

41

Question #4

42

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

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

42

Rabies

43

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

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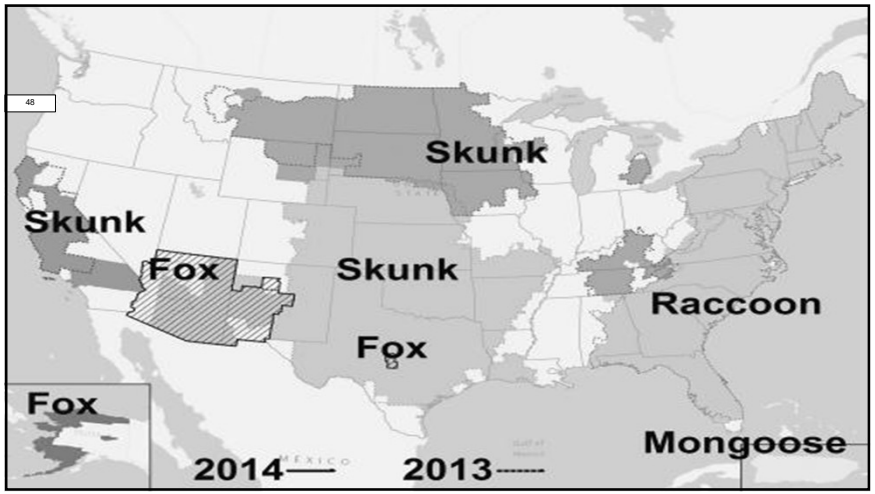

44

Rabies

45

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

45

Rabies

46

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

46

Question #5

47

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

47

Question #5

48

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

48

Question #5

49

Which of the following studies should now be performed?

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

49

Encephalitis
Noninfectious Etiologies

50

- Acute disseminated encephalomyelitis (ADEM)
  - 10-15% of encephalitis cases in US
  - Post-infectious
  - Symptoms 2-4 weeks after trigger
  - MRI bilateral asymmetric T2 hyperintensity in subcortical and deep white matter
- Approximately 20-30% of encephalitis cases are due to autoimmune conditions (e.g., anti-N-methyl-D-aspartate receptor [Anti-NMDAR] encephalitis

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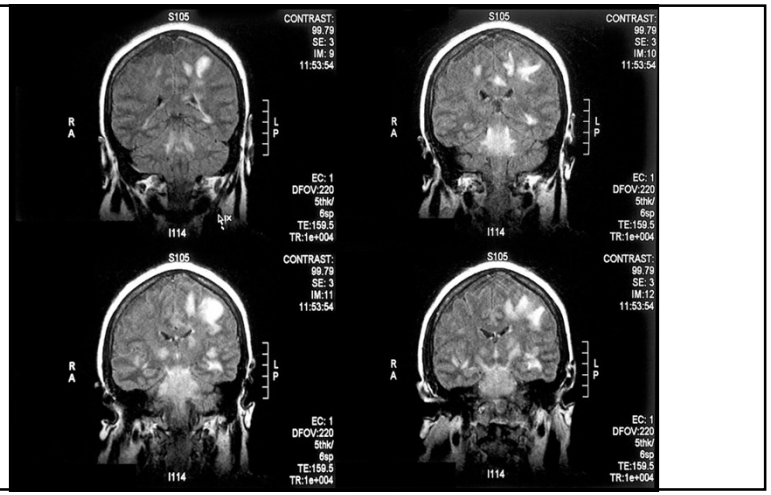

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Anti-NMDAR Encephalitis

52

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

52

Anti-NMDAR Encephalitis

53

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

53

Anti-NMDAR Encephalitis

54

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

*Armangue et al. Brain 2023;146:4306

54

Anti-NMDAR Encephalitis

55

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

55

Anti-NMDAR Encephalitis

56

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

56

57

QUESTIONS

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

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Wednesday, August 20, 2025

48

Staphylococcus Aureus

Henry Chambers, MD

Staphylococcal Diseases – Bacteremia

Henry F. Chambers, MD

Professor of Medicine, Emeritus
University of California, San Francisco

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- Merck – Stock and DSMB member
- Moderna - Stock

2

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

3

Question #1

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

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

4

Predictors of Complicated/High Risk SAB*

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

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

OR = Odds ratio

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

5

Low Risk for Complicated Bacteremia

Absence of **ALL** of the following:

- Community acquisition
- Implanted prosthetic material
- Failure to remove a central venous catheter
- Positive blood cultures beyond 48h on therapy
- Fever ≥ 38ºC for more the 72h on therapy
- Treatment delay for > 48h with signs of infection
- Clinical signs of metastatic infection

Note: Only 9.9% of bacteremias (377/3801); no IVDU, no MRSA; 84% line, skin, 9.1% unknown; median duration of therapy 15 days, 10% infection related mortality/relapse (1) @ 90 days

Hendriks. Clin Infect Dis. 2024; 79:43

6

Question #2

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

7

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

8

Echocardiography (ECHO)

9

Role of Echocardiography for S. aureus Bacteremia

- Prevalence of endocarditis 12%-18% overall
- Depends on the pre-test probability
  - STROBNGLY 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

10

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

- In conjunction with TEE PET/CT increases sensitivity of Duke criteria for definite PVE
- Can identify occult foci of metastatic infection, rule out others
- May improve outcome through better source control and use of longer treatment courses
- Evidence comes entirely from observational studies and subject to bias, such as immortal; time bias

11

Treatment of MSSA Bacteremia

12

Question #3

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

13

FDA-approved Antibiotics for SAB

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

14

Antibiotics for MSSA Bacteremia

Drug	Pros	Cons
Nafcillin, Oxacillin, etc	Proven efficacy, first-line agent	Q4h administration, adverse events are common
Cefazolin	Well, tolerated, q8h dosing, efficacy probably comparable to ASPs	Concern for treatment failure in high inoculum infections
Penicillin	Efficacious, better tolerated than anti-staphylococcal penicillins	Beta-lactamase negative strains only
Vancomycin	Option for patients who are not candidates for beta-lactam therapy, q12h dosing	Less efficacious than beta-lactams, nephrotoxic, requires therapeutic drug monitoring
Daptomycin	Option for patients who are not candidates for beta-lactam therapy, q24h dosing	Probably less efficacious than beta-lactams, treatment-emergence resistance

15

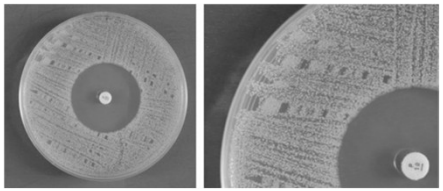
What about Penicillin G for Penicillin-Susceptible SAB? Probably Yes

- Confirm susceptibility
  - MIC $\leq$ 0.025 µg/ml (J Antimicrob Chemother. 2021; PMID: 33615356)
  - MIC $\leq$ 0.12 µg/ml (CLSI breakpoint) and
    - Negative PCR for beta-lactamase gene (blaZ) or
    - Negative zone test
- References supporting efficacy
  - J Antimicrob Chemother. 2023; PMID: 37596905
  - Int J Antimicrob Agents. 2022; PMID: 35288257
  - Int J Antimicrob Agents. 2019; PMID: 31181352

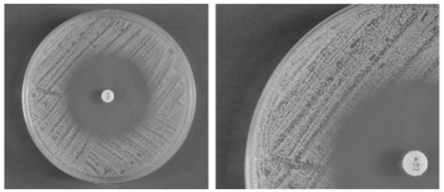
16

Zone Edge Test for β-lactamase

Positive



Negative



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Summary: MSSA bacteremia

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

*ASP = antistaphylococcal penicillin

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Treatment of MRSA Bacteremia

19

Therapy for MRSA bacteremia

- Vancomycin
  - Dosed at 30-60 mg/kg/d
  - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
  - Need for therapeutic drug monitoring
- Daptomycin
  - FDA approved dose: 6 mg/kg q24h, recommended dose: 10 mg/kg q24h
  - Non-inferior to vancomycin, better tolerated
  - Potential for emergence of resistance on therapy (mprF mutants), especially in high inoculum infections, poor source control
  - Do not use for primary pneumonia (OK for septic emboli)
  - Some cross-resistance with VISA
- Ceftobiprole – recently FDA approved

Tong, et al: JAMA. 2025. PMID: 40193249

20

Vancomycin or Daptomycin?

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

Int J Antimicrob Agents. 2023, 62:106946

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Other Antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome; bacteriostatic Bone marrow suppression
Ceftaroline	SSTI, CAP	Rash, usual cephalosporin reactions, neutropenia
Dalbavancin	SSTI	Single dose or 2 doses a week apart Lipoglycopeptide, related to teicoplanin
Ceftobiprole	FDA approved SSTI, SAB	Non-inferior to daptomycin in RCT of MSSA and MRSA bacteremia (NEJM 2023;389:1390)

SSTI = skin and soft tissue infection, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia
CAP = community-acquired pneumonia

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Question #4

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

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But What About That Vancomycin MIC Of 2 Mg/Ml?

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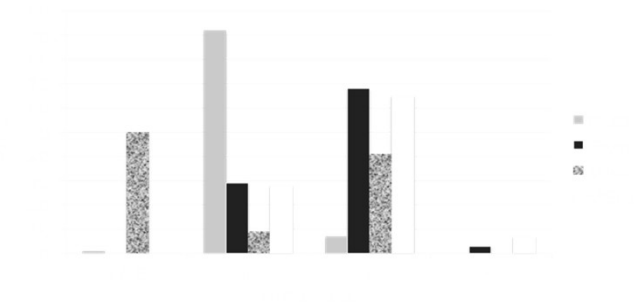
Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

25

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

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Duration of Therapy for S. aureus BSI

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Duration of Therapy for S. aureus BSI

14 days	• UNCOMPLICATED/LOW RISK (~20% of cases) • Fever resolves by day 3 • **Sterile blood culture after 1-2 days (DOCUMENT!)** • **Easily removed focus of infection (no DVT)** • **No metastatic infection (e.g., osteo)** • **Neg. echo, no evidence of endocarditis, no abnormal valve** • No implanted prosthetic devices, no DM, no immunosuppression
4-6 weeks +	• COMPLICATED/HIGH RISK • Failure to meet one or more of above criteria • Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

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Oral Therapy of S. aureus BSI

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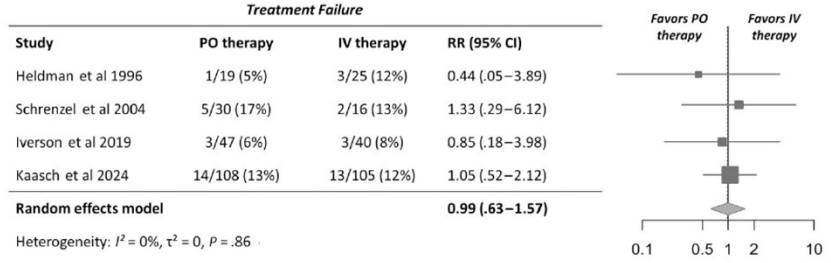
Meta-Analysis: Oral Therapy of S. aureus Bacteremia



Study	PO therapy	IV therapy	RR (95% CI)
	Treatment Failure		
Heldman et al 1996	1/19 (5%)	3/25 (12%)	0.44 (.05–3.89)
Schrenzel et al 2004	5/30 (17%)	2/16 (13%)	1.33 (.29–6.12)
Iverson et al 2019	3/47 (6%)	3/40 (8%)	0.85 (.18–3.98)
Kaasch et al 2024	14/108 (13%)	13/105 (12%)	1.05 (.52–2.12)
Random effects model			**0.99 (.63–1.57)**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .86$

Clin Infect Dis. 2025; 80:29.

30

SABATO RCT: Oral Step-down vs IV for "Low Risk" SAB

- 5063 patients screened, 4696 did not meet eligibility criteria, 206 enrolled
- 5-7 days IV
  - Flucloxacillin, cloxacillin, cefazolin, vancomycin for MSSA
  - Vancomycin or daptomycin for MRSA
- Randomized at day 5-7 to complete 14 days of therapy
  - IV regimen as above **OR**
  - Oral regimens: TMP/SMX 160/80 mg q12h (MSSA, MRSA) or Clindamycin 600 mg q8h (MSSA) or Linezolid 600 mg q12h (MRSA)
- 8% MRSA
- 90% central (23%) or peripheral catheter (44%), skin, soft tissue infection (23%)
- Study terminated at 50% planned enrollment, 10% (vs original 2.5%) non-inferiority margin

TMP/SMX = trimethoprim/sulfamethoxazole

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

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

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

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

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Question #5

A Case of MSSA Bacteremia

37-year-old M, diabetic, moderate chronic kidney disease, admitted to the intensive care unit for diabetic ketoacidosis. Internal jugular central line placed.

D3: awaiting transfer to the floor he spikes a fever to 38.9oC, P 105, vital signs otherwise normal. Non-focal exam. Chest x-ray negative, urine 2+ protein. Blood culture (BC) x2 sent, vancomycin and cefepime begun.

D4: Both D3 BC+ GPCs (Gram-positive cocci) in clusters. BCx2 sent. Afebrile.

D5: D3 BC+ MSSA, penicillin resistant. D4 2/2 BC+ GPCs in clusters. BCx2 sent, central line removed, and antibiotics changed to cefazolin.

D6: D4 BC+ MSSA, 1 of 2 D5 BC+ for GPCs in clusters. BCx2

D7: 1 of 2 D5 BC+ MSSA, D6 BC no growth. BCx2 sent.

D8-10: TTE negative. D6 BC and all subsequent BC no growth.

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Question #5

Which one of the regimens would you recommend for definitive therapy of the MSSA bacteremia?

A. 7 days of cefazolin IV then clindamycin 600 mg PO TID for 7 days
B. 14 days of cefazolin IV
C. 14 days of cefazolin IV then clindamycin 600 mg PO TID for 7 days
D. 14 days of cefazolin IV then clindamycin 600 mg PO TID for 14 days
E. 28 days of cefazolin IV

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Oral Therapy of S. aureus Bacteremia

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

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Combination Therapy of S. aureus BSI

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Question #6

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

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Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA,MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs, RCT	MRSA,MSSA	1d shorter SAB, toxic	Various
Adjunctive dapto	RCT	MSSA	No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
Dapto + ceftaroline	Obs, aborted RCT	MRSA	Low quality data	30858203 31640977 31404468
Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985
β-lactam + ertapenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration ↓ by 25h	38946294

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

38

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA,MSSA	No benefit	
Adjunctive aminoglycoside	Obs, RCT	MRSA,MSSA	1d shorter S… …ious	
Adjunctive dapto	RCT	MSSA		32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	…, higher mortality	32044943
Dapto + ceftaroline	Ob…		Low quality data	30858203 31640977 31404468
Dapto + f…	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985
…ertapenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration ↓ by 25h	38946294

Consider for salvage therapy, not first line

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

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De-escalation of Combo Therapy for Complicated MRSA bacteremia

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

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

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Take-Home Points

- "Uncomplicated" Bacteremia is uncommon
  - TTE for all
  - 2 weeks of therapy for "low risk" SAB, otherwise 4-6 weeks
- Parenteral drugs of choice
  - MSSA: Nafcillin, cefazolin, penicillin
  - MRSA: Daptomycin, vancomycin
- Role of oral therapy is an evolving area
- Monotherapy is effective in most cases, reserve combination therapy for salvage

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Thanks

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Wednesday, August 20, 2025

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Bone and Joint Infections

Sandra Nelson, MD

Bone and Joint Infections

Sandra B. Nelson, MD

Massachusetts General Hospital
Harvard Medical School

7/25/2025

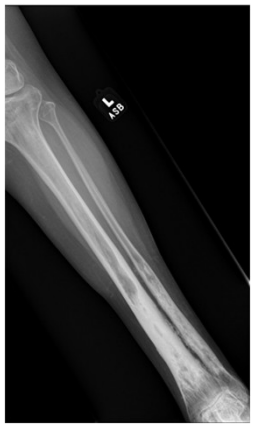
1

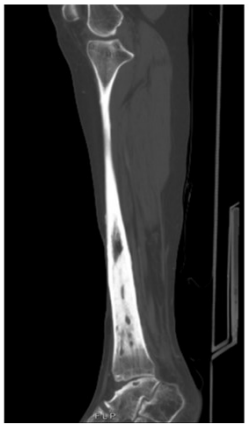
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Osteomyelitis





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Osteomyelitis: Unifying Principles

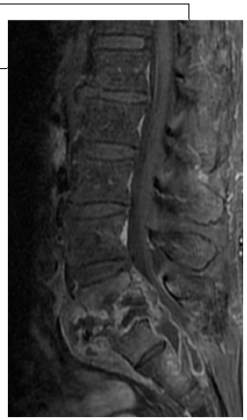
- Diagnosis can only be confirmed through bone histopathology and culture
- Imaging studies:
  - MRI is the most sensitive imaging study for diagnosis
  - Serial plain films and CT are more useful in subacute and chronic infection (bony erosion)
  - Bone scan is an excellent "rule-out" test; should never be used to confirm infection
  - Imaging studies not useful as a test of cure
- Optimal therapy remains an evolving target
  - 6 weeks of antimicrobial therapy commonly used
  - Oral therapy increasingly supported
  - Longer oral suppression in setting of retained hardware

4

4

Question #1

- 57-year-old male presented with 3 months of progressive lower back pain.
- He denied fevers or chills, but his wife noticed weight loss
- Born in Cambodia, emigrated to U.S. as a child
- ESR 84 CRP 16
- MRI with discitis and osteomyelitis at L5-S1
- Blood cultures grew *Staph epidermidis* in 2 of 4 bottles



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Question #1

What is the best next step in management?

A. Repeat 2 sets of blood cultures
B. Obtain interferon gamma release assay
C. Percutaneous biopsy of disc space
D. Initiate vancomycin; place PICC for six-week treatment course
E. Empiric treatment with rifampin, isoniazid, ethambutol, and pyrazinamide

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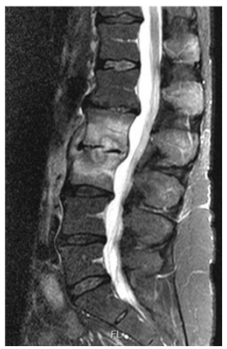
Vertebral Osteomyelitis: Diagnosis



- Imaging pearls
  - MRI most sensitive in early infection
  - Infection almost always involves two contiguous vertebral bodies
- Blood cultures often positive in early infection
  - No further diagnostics if *Staph aureus* or *Staph lugdunensis*
- Brucella serologies, PPD/IGRA when appropriate epidemiology
- Percutaneous biopsy when blood cultures negative
  - Hold antibiotics 1-2 weeks prior if no sepsis or neurologic compromise

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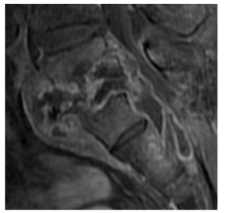
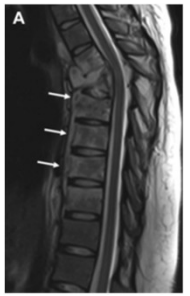
Pott's Disease



- Clinical:
  - More indolent than pyogenic osteomyelitis
  - Constitutional symptoms common
- Radiographic:
  - Thoracic>lumbar with anterior involvement
    - Anterior collapse may lead to gibbus deformity
  - Relative sparing of the disc space until late
  - Multi-level disease, large paraspinal abscesses
- Treatment:
  - Conventional TB therapy, 6-12 months
  - Surgery often not necessary



Simpfendorfer Infect Dis Clin N Am 2017;31:299

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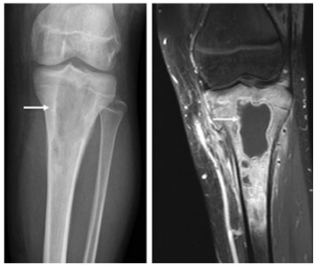
Brodie's Abscess: Subacute hematogenous osteomyelitis

- More common in children and young adults
- Bacteria deposit in medullary canal of metaphyseal bone, become surrounded by rim of sclerotic bone → intraosseous abscess
- "Penumbra sign" on MRI
  - Granulation tissue lining abscess cavity inside bone gives appearance of double line
- *Staph aureus* most common



Simpfendorfer Infect Dis Clin N Am 2017;31:299

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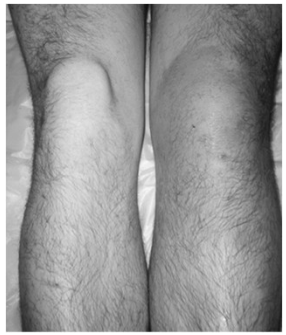
Septic Arthritis



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Question #2

A previously healthy 29-year-old woman developed acute right thumb pain followed by bilateral ankle pain and swelling, leading to inability to ambulate. She had no relief with NSAIDs and presents to the ED.

On exam, she is afebrile. The right thumb MCP joint was erythematous and warm, and there were bilateral ankle effusions. She guards against movement of the thumb and ankles.

Plain films showed bilateral tibiotalar effusions

Laboratory Studies
WBC 13,000 (72% pmns)
ESR 62 CRP 47.7 mg/L
ANA 1:40, speckled pattern

Synovial Fluid Sampling (right ankle):
34,500 WBCs/μL (83% neutrophils)
Negative gram stain
No crystals

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Question #2

While synovial fluid cultures are pending, what is the next best step?

A. Measure anti-citrullinated peptide antibody
B. Obtain HLA-B27 test
C. Initiate treatment with systemic glucocorticoids
D. Obtain blood cultures, cervical NAAT testing, and initiate vancomycin and ceftriaxone
E. Bilateral ankle arthrotomy and debridement procedures

NAAT: Nucleic Acid Amplification test

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Septic Arthritis: Clinical Pearls

- Synovial fluid cell counts: No diagnostic threshold
  - Higher probability of SA if WBC >50,000/mm^3
  - Lower cell counts do not exclude septic arthritis
- More subtle presentations in immunocompromised hosts and with indolent organisms
  - Subacute history
  - Lower synovial fluid cell counts
- Negative cultures and/or delayed culture positivity:
  - think Gonococcus, HACEK, Lyme, Mycoplasma

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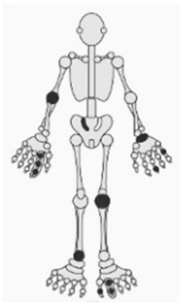
Joint Involvement



Majority of septic arthritis is monoarticular (knee in 50%)
- Axial joints (e.g. sternoclavicular): think PWID
- Sacroiliac joint: think PWID, Brucella

10-20 % of septic arthritis is oligo- or polyarticular
- Associated with bacteremia/sepsis
  - Staph aureus most common (look for endocarditis)
- Also seen in immunocompromised hosts

Other causes of polyarthritis
- Rat bite fever
- Disseminated gonococcus
- Viral infection
- Non-infectious

PWID: Persons who inject drugs

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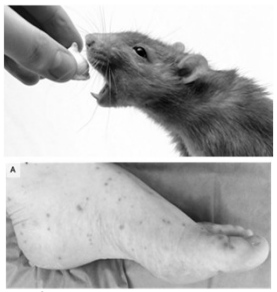
Rat Bite Fever

- Seen in children, laboratory technicians
- Polyarthritis (usually symmetric, often migratory),
- Associated with fever, maculopapular and/or pustular rash
- *Streptobacillus moniliformis* (or if bitten in Asia – *Spirillum minus)*
- Rx: penicillin



Giorgiutti NEJM 2019: 381:1762

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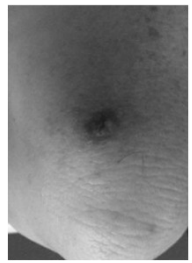
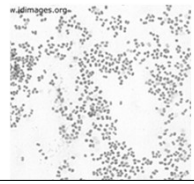
Gonococcal Arthritis

- Tenosynovitis, arthralgias, skin lesions
  - Especially extensor surface tenosynovitis
  - Migratory arthralgias
- Purulent arthritis
  - May be polyarticular; knees most common
  - Lower synovial fluid cell counts more common
- Asymptomatic mucosal phase predisposes
  - Dissemination more common in women
- Dx: mucosal site sampling (cervical, urethral) is highest yield
  - Blood (<30%) and synovial fluid (<50%) cultures lower yield
  - Compatible clinical syndrome





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Viral Arthritides

- Symmetric polyarthritis, often involving small joints
- Often associated with fever and rash
- Diagnose serologically (+IgM or 4-fold rise in IgG titer) or by viral pcr

Most common viruses to cause arthritis	Clinical and Epidemiologic Clues
Parvovirus B19	More common in women. History of exposure to young children, often a teacher or parent. Hands most common; can be severe.
Rubella	Non-immune (non-US born). See cervical lymphadenopathy, fever, rash.
Hepatitis B Virus	Serum-sickness like reaction, resolves with development of jaundice; also polyarteritis nodosa (PAN)
Hepatitis C Virus	Immune complex arthritis associated with cryoglobulinemia
Alphaviruses (esp. Chikungunya)	Travel to endemic areas

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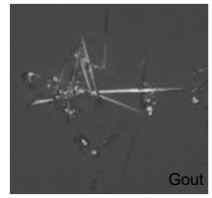
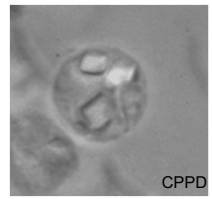
Crystalline Arthritis: Clinical Pearls

- Acute gout mimics septic arthritis
  - Fever common
  - Monoarthritis and polyarthritis forms
  - Clues: rapid onset (hours), history of prior gout, alcohol, CKD, diuretics, elevated uric acid
  - Synovial WBC 10,000-100,000/mm^3
  - Needle-shaped monosodium urate crystals
- CPPD less likely to mimic septic arthritis
  - Crystalline disease and septic arthritis can coexist (esp. CPPD)
  - CPPD rarely has cell count >30,000
  - CPPD rarely associated with high fever
  - Rhomboid-shaped calcium pyrophosphate dihydrate crystals


Gout


CPPD

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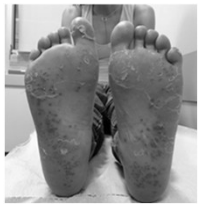
Masquerading as Infection…

Many noninfectious causes of arthritis:

- Reactive arthritis
  - Following enteric or genitourinary infection
  - Asymmetric mono or oligo-arthritis affecting knees/ankles
  - Associated features: enthesitis (tendon insertion), dactylitis (sausage digits), mucosal lesions, urethritis, conjunctivitis/uveitis, skin lesions (keratoderma blennorhagica)
- Still's disease
- Sarcoid (Lofgren's)
- Polymyalgia rheumatica ….



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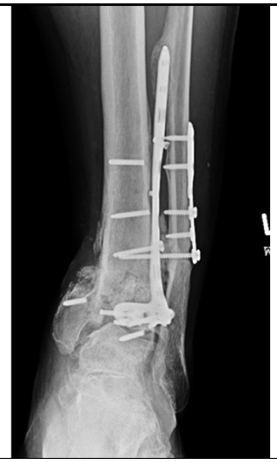
Fracture-related Infections



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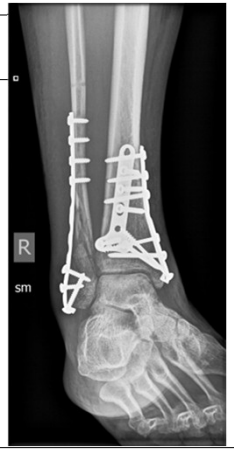
Question #3

- 44-year-old healthy woman suffered a right ankle closed pilon fracture and underwent open reduction and internal fixation (ORIF)
- Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole
- Two months after ORIF, superficial wound culture grows methicillin-susceptible *Staph aureus*
- Plain films: Hardware intact; fracture not yet consolidated



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Question #3

What are your next steps?

A. No surgical debridement; cefazolin for 6 weeks
B. Surgical debridement with hardware removal; 6 weeks of cefazolin
C. Surgical debridement with hardware removal; 6 weeks of cefazolin and rifampin
D. Surgical debridement without hardware removal; 6 weeks of cefazolin and rifampin
E. Surgical debridement with hardware exchange; 6 weeks of cefazolin and rifampin

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Fracture-related Infections

Goals include both fracture consolidation and infection eradication
Removal of hardware depends upon fracture healing and stage
Antibiotic choice and duration not well studied

	Early infections prior to fracture union	Late nonunion	Late, healed fracture
Surgical Strategy	Debride and retain (assuming implants well fixed)	Hardware removal Revision or external fixation	Hardware removal
Antimicrobial Management	Pathogen-directed therapy Addition of rifampin if Staph Duration often 12 weeks or until fracture heals	Pathogen-directed therapy Duration often six weeks	Pathogen-directed therapy Duration often two weeks following hardware removal

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Oral Antibiotics for Bone and Joint Infections

- Now supported by a large body of literature for definitive therapy of bone and joint infection
  - Caution with life- or limb-threatening infections
- Usually after an IV lead-in and after clinical response
- Relative contraindications/exclusions:
  - Lack of suitable oral option
  - Other indication for IV treatment (e.g. endocarditis and bacteremia)
  - Not well studied for drug-resistant bacteria (e.g. MRSA)
  - Concern for malabsorption
- Little data to support "bone-penetrating antibiotics"
  - Some advantage to quinolone + rifampin in Staphylococcal PJI

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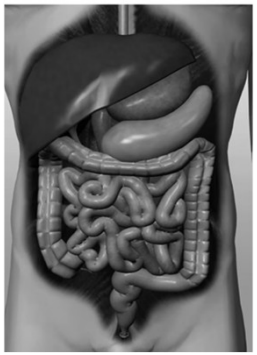
Highly Bioavailable Oral Therapy



- Amoxicillin
- Cefadroxil / cephalexin*
- Ciprofloxacin / levofloxacin / moxifloxacin
- Clindamycin
- Doxycycline / minocycline*
- Linezolid
- Metronidazole
- Rifampin
- Trimethoprim-sulfamethoxazole

*Oral cephalosporins and tetracyclines not as well studied in bone and joint infection

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Rifampin in Orthopedic Infections

- Considered a “biofilm active” agent
- Best studied for Staphylococcal PJI in setting of hardware retention
  - Data extrapolated for other hardware infections (osteofixation, spinal implant)
- Specifics
  - Never to be used in monotherapy of established infection
  - Should not be used prior to surgical debridement and until partner drug therapeutic
  - Multiple drug interactions (primarily via Cyp 3A4 pathway)

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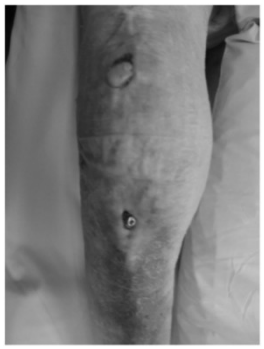
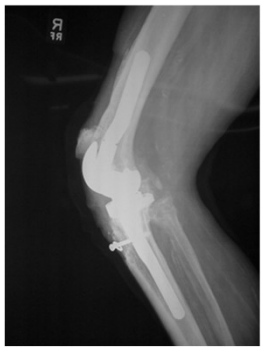
Prosthetic Joint Infection (PJI)





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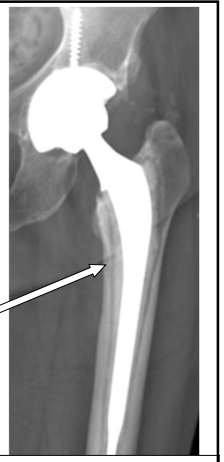
PJI: Diagnostic Pearls

- Diagnosis of early and late hematogenous PJI usually straightforward
- Multiple diagnostic algorithms have been developed for chronic PJI
- Diagnosis of chronic PJI confirmed if:
  - Sinus tract to the joint
  - Two synovial fluid or tissue cultures positive with the same organism

	Early PJI and Late hematogenous	Delayed (chronic) PJI
ESR/CRP	High	Normal or moderately elevated
Plain films	May be normal or show effusion	May be normal or show periprosthetic lucency
Synovial fluid cell counts	WBC > 10,000/µL % pmns > 90	WBC > 3000/µL % pmns > 70
Synovial fluid Alpha-defensin	Usually positive	Usually positive



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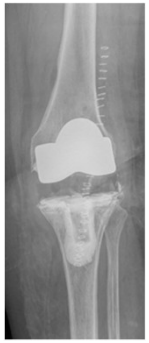
PJI: Management



Surgical Procedure	Indication	Antimicrobial Therapy
Debridement and implant retention (exchange of modular components)	Early surgical site infection Acute hematogenous Well-fixed components	6 weeks antibiotics (IV/PO) Continued oral antibiotics to complete 3-6 months Rifampin if Staph
1-stage exchange	Acute and subacute infections Healthy soft tissues Sensitive organisms	6 weeks antibiotics (IV/PO) Continued oral antibiotics to complete 3 months Rifampin if Staph
"2-stage" exchange Antibiotic spacer (With or without 2nd stage)	Chronic infections Sinus tracts Resistant organisms	6 weeks antibiotics (IV/PO)

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Question #4

A 57-year-old woman underwent total hip arthroplasty

- She never achieved a pain-free state after surgery

Eighteen months postoperatively, she was diagnosed with delayed periprosthetic infection due to *Enterococcus faecalis*

- Sensitive to ampicillin, vancomycin, linezolid, daptomycin, gentamicin

Her orthopedist plans a two-stage exchange procedure utilizing a temporary spacer comprised of polymethylmethacrylate (PMMA)

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Question #4

You are asked to provide recommendations about systemic and local antimicrobial therapy for the spacer. She has no antimicrobial allergies.

What would you advise?

A. Ampicillin in the cement; systemic vancomycin
B. Ampicillin in the cement; systemic ampicillin
C. Gentamicin in the cement; systemic ampicillin
D. Tobramycin in the cement; systemic daptomycin
E. Ceftriaxone in the cement; systemic linezolid

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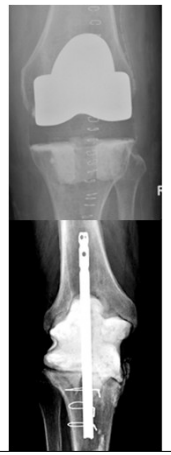
Antimicrobial Cement (PMMA)

- "Spacer" serves mechanical role
  - Joint stability, allows mobility, prevents contractures
- Elution: high levels within the first few days
  - Local tissue concentration exceeds systemic delivery
  - May elute for months or longer
- Antimicrobial considerations
  - Known or suspected organisms
  - Thermal stability (avoid most β-lactams)
  - Osteocyte toxicity (avoid quinolones)
  - Vancomycin and aminoglycosides most common
  - Toxicity and allergy reported but rare



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Prevention of PJI

- Immunosuppressives:
  - Stop biologics, no need to stop DMARDs or low dose prednisone
- Surgical antibiotic prophylaxis: one dose prior to surgery
- Urinary tract infections:
  - Diagnose and treat symptomatic UTI
  - Do not screen for asymptomatic bacteriuria
- Dental prophylaxis: no more!
- *Staph aureus* decolonization reduces surgical site infection

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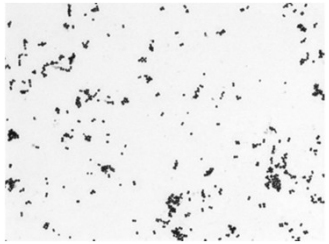
Microbiology of Musculoskeletal Infections



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Question #5

A 56-year-old man with poorly controlled diabetes presents to ED with a one-week history of low-grade fevers and gradually progressive right knee pain and swelling. He traveled to the Dominican Republic one month ago and had no illnesses while traveling. He last saw a dentist six months ago and denies tooth pain. There is no history of injection drug use.

On exam he has a moderate effusion and pain with passive range of motion of the knee. His ESR (68) and CRP (17 mg/dL) are elevated, and synovial fluid is inflammatory (45,000 WBCs, with 82% neutrophils) with a negative gram stain.

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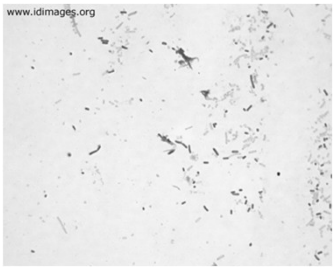
Question #5

Culture growth at 3 days incubation



What is the most likely organism?

A. *Serratia marcescens*
B. *Salmonella heidelberg*
C. *Staphylococcus aureus*
D. *Kingella kingae*
E. *Pasteurella multocida*

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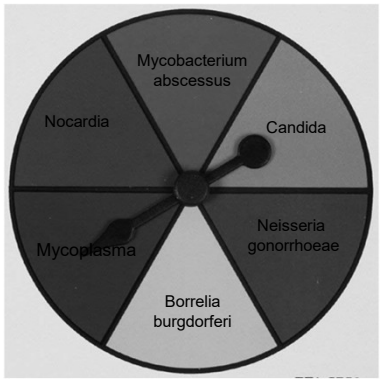
Guess the Bug

Musculoskeletal Edition



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Salmonella Species

- Clinical
  - Seen in sickle cell disease, immunocompromised, diabetes
  - Hematogenous infection (septic arthritis, spondylodiscitis, long bone infection)
- Epidemiology
  - Reptile exposure
  - Travel to developing world
  - Unsafe food hygiene

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Serratia and Pseudomonas

- Risk Factors
  - Injection drug use (tap water)
  - Immunocompromised host
  - Indwelling lines
- Clinical factors
  - Usually hematogenous
  - Predilection for sacroiliac and sternoclavicular joints in injection drug use

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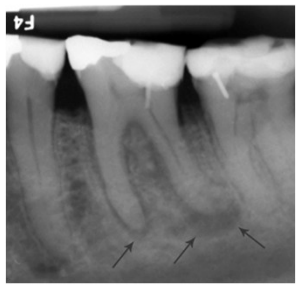
HACEK Organisms



- Clinical
  - Usually hematogenous
- Epidemiology
  - Antecedent mouth trauma, gum or dental infection, or dental procedure
  - Odontogenic infection may be silent
- Microbiology
  - Late growth in culture, may be culture negative
- *Kingella kingae*
  - Most common cause of osteoarticular infection in young children; diagnosed by PCR

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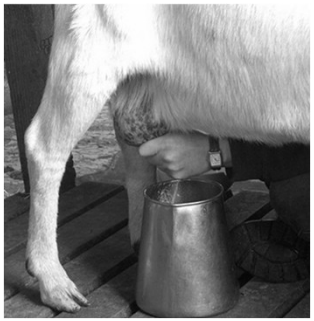
Brucella Species



- Clinical
  - Fevers often precede musculoskeletal symptoms
  - Septic arthritis with predilection for sacro-iliac joint
  - Also causes spondylodiscitis
- Epidemiology
  - Endemic in Latin America, Mediterranean, Middle East, parts of Asia
  - Consumption of unpasteurized dairy most common
- Microbiology
  - Small gram-negative coccobacillus; grows late in culture
  - Laboratory biohazard
  - Serologies helpful in non-residents of endemic areas

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Pasteurella Species

- Clinical
  - Direct inoculation (bite)
  - Hematogenous spread
  - Rapid clinical onset
- Epidemiology
  - Exposure to cats/dogs
  - Bite history not always elicited in hematogenous infection

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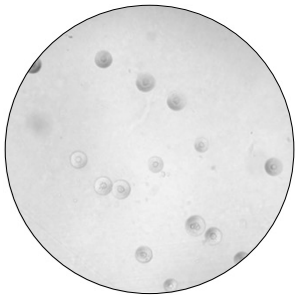
Mycoplasma hominis

- Host factors
  - Immunodeficiency, especially humoral (CVID, XLA)
  - Postpartum women
- Clinical factors: hematogenous infection
- Microbiology
  - Difficult to grow in routine culture
  - "Fried egg" morphology in culture



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Borrelia burgdorferi (Lyme)

- Clinical
  - Large effusions; some resolve over weeks but may recur
  - Warmth and swelling out of proportion to pain
  - Mono-arthritis of the knee most common
- Epidemiology
  - Northeast U.S. and upper mid-west with tick exposure
- Micro: culture-negative
  - Diagnosed serologically or with synovial fluid Borrelia PCR

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Non-tuberculous Mycobacteria

- Clinical
  - Slowly progressive tenosynovitis; can spread to bones and joints
  - May be accompanied by nodular lymphangitis
  - May cause polyarthritis in immunocompromised hosts
- Epidemiology
  - Environmental sources of water
  - Marine injury/trauma
  - Fish-tank exposure
  - Medical tourism
- Microbiology
  - Some organisms (marinum) grow better in cooler temperatures

45

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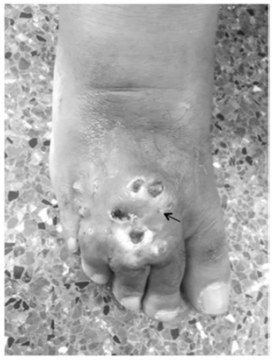
Yeasts and Molds

- Clinical
  - May be contiguous inoculation or hematogenous spread
  - Often more indolent than bacterial organisms
  - In the spine may mimic tuberculosis
- Epidemiology
  - Candida: injection drug use, indwelling lines, immunocompromise, antibiotic exposure
  - Molds: soil contamination (trauma), barefoot walking (Madura foot), immunocompromise (neutropenia), medical tourism



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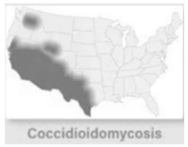
Endemic Mycoses

- Coccidiodes and Blastomyces > Histoplasma
- Clinical
  - Subacute septic arthritis and long bone osteomyelitis
  - May see draining sinuses adjacent to osteomyelitis
  - In spine, may also mimic tuberculosis
  - Host immunocompromise more common in coccidioides
  - May see concomitant pulmonary infection



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Thank you!

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49 Bone and Joint Infections

Speaker: Sandra Nelson, MD

Wednesday, August 20, 2025

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Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Kevin Winthrop, MD

Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Kevin L. Winthrop, MD, MPH

Professor, Divisions of Infectious Diseases, Public Health and Preventive Medicine
Oregon Health & Science University

7/25/2025

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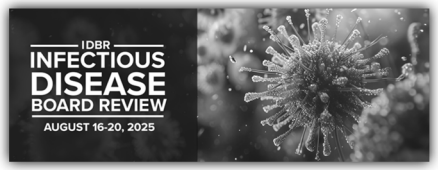

Disclosure of Financial Relationships with Relevant Commercial Interests

- Research Grant---Insmed, Spero, Paratek, AN2, Mannkind
- Consultant--- Insmed, Spero, Paratek, AN2, Mannkind

2

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

3

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)*

4

NTM Disease Clinical Manifestations

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

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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*

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Important Bug-Setting Associations

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

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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

8

Question #1

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

9

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)

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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

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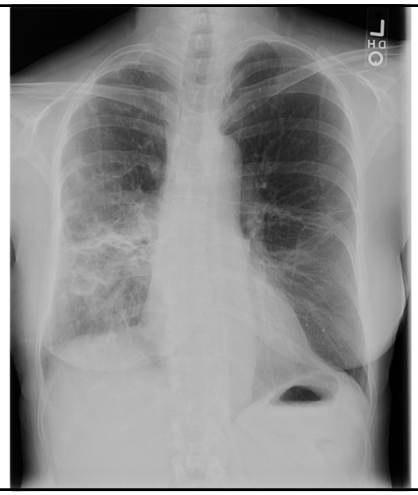

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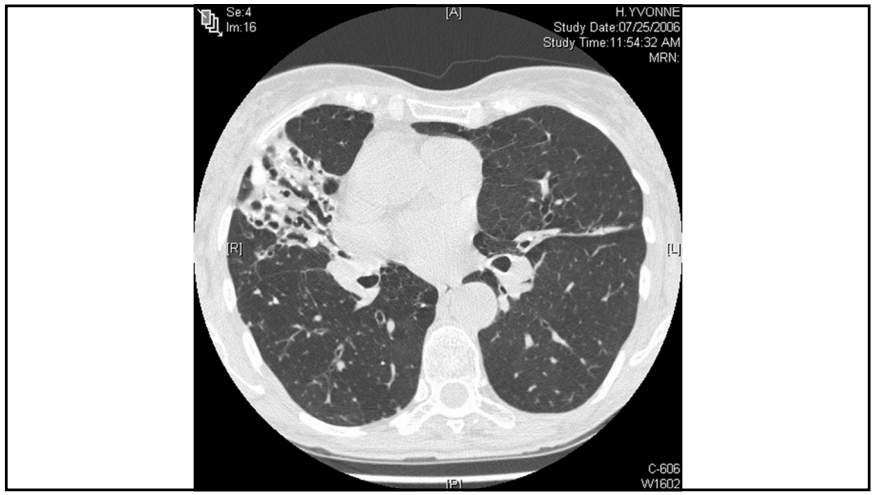

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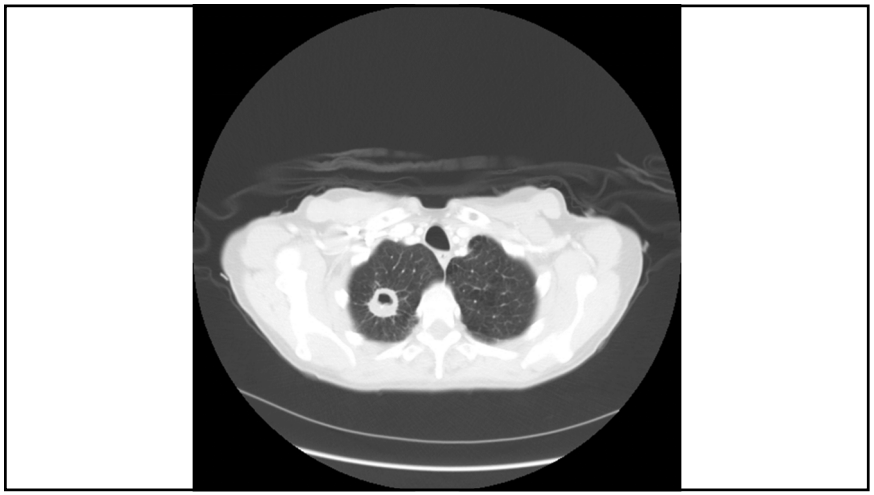

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Pulmonary NTM Risk Factors

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

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NTM Pulmonary Disease Diagnosis

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

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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

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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.
    - FQ or Macrolide useful in RIF resistant disease

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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

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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), Omadacycline 300mg QD
  - Surgical resection

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Extrapulmonary NTM

1. Immunocompetent settings
2. Immunocompromised settings

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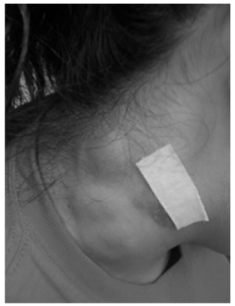
Immunocompetent settings

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

22

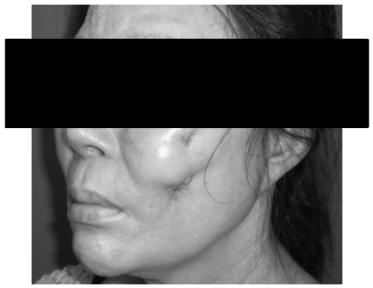
Children under 5 years NTM > TB



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

23

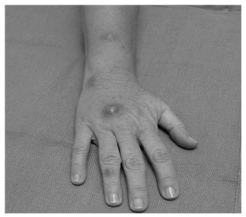
Post-plastic Surgery

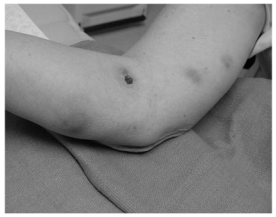


- Usually Rapid Grower:
  - *M. chelonae*
- Remove foreign-bodies
- Therapy as per in-vitro susceptibility
- Length 4-6 months

24

M. marinum---fish tank granuloma





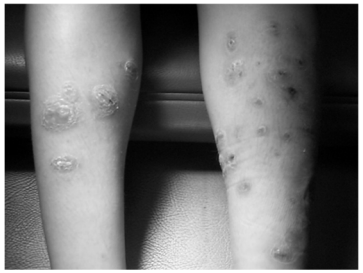
Treatment: multiple drugs

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

25

Nail Salon Furunculosis

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



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Tattoo-associated

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

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Question #2

20-year-old 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

Based on the most likely diagnosis, which of the following would you recommend?

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

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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)

Griffith D et al. AJRCCM 2007

TABLE 7. REGIMENS FOR TREATMENT AND PREVENTION OF DISEMINATED *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.

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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

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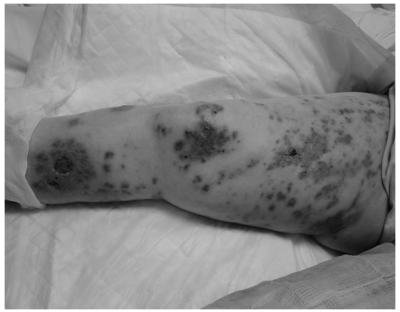
M. chelonae in cancer patient



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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

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M. chimaera

- Slow growing. M. avium complex
  - Pulmonary disease
- 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?

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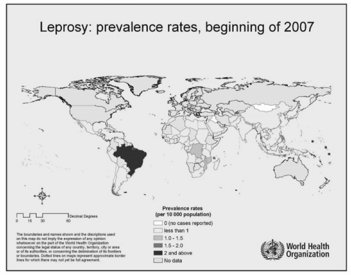
Hansen's Disease (Leprosy)

- 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



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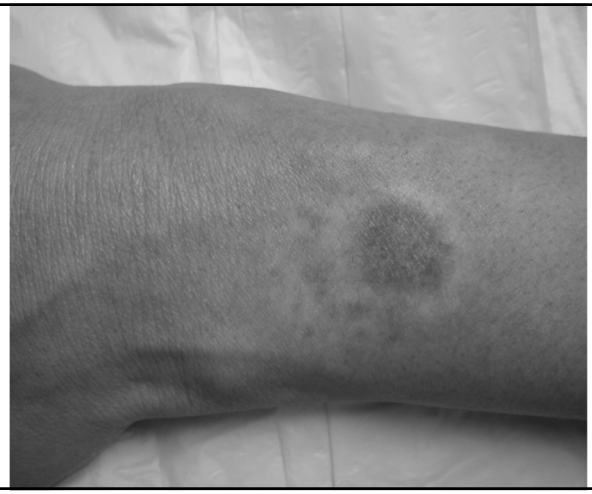
Leprosy Disease Classification

- 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

35



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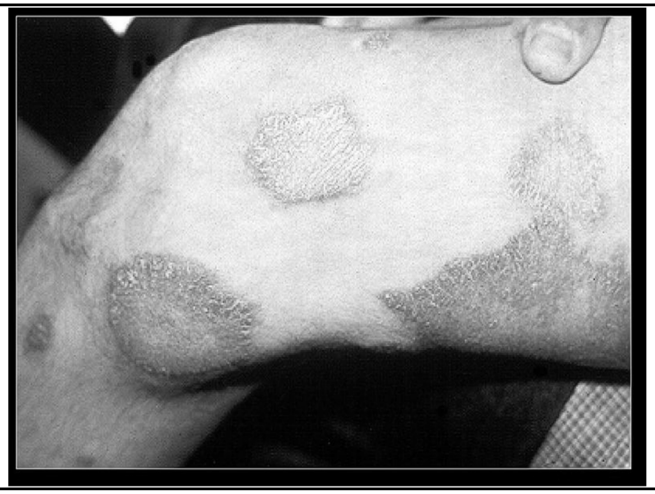

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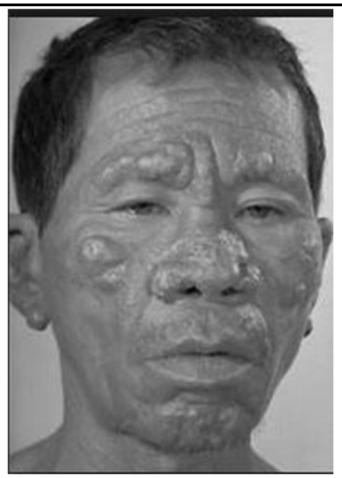

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Leprosy Treatment

- PB (6-12 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - *Rifampin 600mg once monthly
- (US guidelines are daily RIF and no Clofaz for 12 months)

- MB (12-24 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

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

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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

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Wednesday, August 20, 2025

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Infections in Solid Organ Recipients

Barbara Alexander, MD

Infections in Solid Organ Transplant Recipients

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7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant:** Scynexis, GSK, Astellas, Pulmocide, HealthTrackRx, Basilea, TFF Pharma
- **Research Grant to My Institution:** Karius
- **Clinical Trials (Site PI/Study PI):** Scynexis, F2G
- **Royalties (Chapter Author):** UpToDate

2

Infections in Solid Organ Transplant (SOT) Recipients

- SOT is a life-saving intervention
  - 1,032,217 SOTs performed in U.S. since 1988
  - 48,149 SOTs performed in 2024
  - ~40% increase over past decade
- SOT recipients
  - Have compromised immunity / increased infection risk
  - Are targets for common, emerging & opportunistic pathogens encountered pre- and post-transplant
  - Often have atypical infection presentation owing to their compromised immunity / decreased inflammatory response
  - Are on complex medical regimens; drug interactions common

Data from Organ Procurement and Transplantation Network database as of May 19, 2025

3

What You Should Know for the Board Exam

- Infection risk varies based on
  - Organ transplanted
  - Time post transplant
  - Degree of immunosuppression
  - Prophylaxis regimen
  - Unique exposures
- Key drug interactions and drug-induced syndromes
  - Calcineurin inhibitors and azoles, macrolides, rifampin (covered in another lecture)
  - Sirolimus associated pneumonitis
  - Calcineurin inhibitors and TTP and PRES

4

What You Should Know for the Board Exam

- The following major clinical syndromes:
  - CMV syndrome & disease
  - EBV & Post Transplant Lymphoproliferative Disorder (PTLD)
  - BK virus nephropathy
  - Aspergillosis, Mucormycosis & Cryptococcosis
  - Tuberculosis
  - Toxoplasmosis
  - Donor-derived infections

5

Play the Odds

The data in the stem let's you "play the odds" as to the most likely diagnosis

- Patient completing valganciclovir prophylaxis 6 weeks prior presenting with fatigue, low grade fever and leukopenia
  - CMV
- Donor died from skiing accident in freshwater lake in Florida and recipient presents 3 weeks post transplant with encephalitis
  - Naegleria
- Renal transplant recipient on valganciclovir prophylaxis presents with asymptomatic renal dysfunction
  - BK Virus
- Lung transplant recipient planted vegetable garden 2 weeks prior while on posaconazole prophylaxis and presents with productive cough and cavitary lung lesion
  - Nocardia

6

Frequency, Type & Infection Source in the 1st Post Transplant Year

Transplant Type	Infection Episodes per Patient	Bacteremia	CMV Disease * (%)	Fungal Infections (%)	Most Common Source
Lung	3.19	8-25	39	8.6	Pulmonary
Liver	1.86	10-23	29	4.7	Abdomen & Biliary tract
Heart	1.36	8-11	25	3.4	Pulmonary
Kidney	0.98	5-10	8	1.3	Urinary tract

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

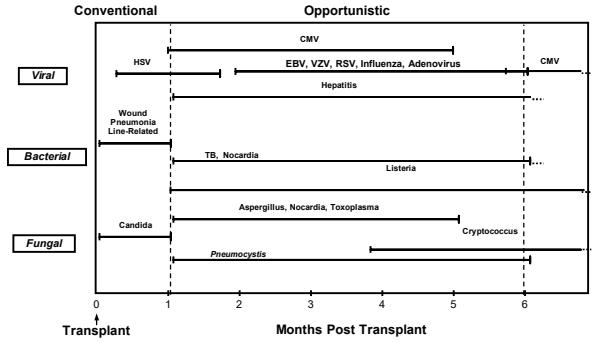
Table Modified from: Principles and Practices of Infectious Diseases, 8th Edition. Chapter 313: Infections in Solid-Organ Transplant Recipients by Nina Singh and Ajit Limaye. Editors: Bennett JE, Dolin R, and Blaser MJ. Elsevier Saunders, Philadelphia, PA, 2015.

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

7

Classic Timing of Infections Following Solid Organ Transplantation

Timing altered by:
- Enhanced immunosuppression
- Prophylaxis regimen
- Unique exposures



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"Early" Bacterial Infections Following SOT

Type & site of early bacterial infection varies based on organ transplanted, surgical approach/technique & transplant center

- Risk of peritoneal soilage/infection greater in liver transplantation with Roux-en-Y biliary drainage
- Recipient colonization with resistant organisms (e.g. MRSA, VRE, CRE) pre-transplant, confers risk of post-transplant infection
- Cluster with unusual pathogen - environmental problem? (e.g., *Legionella, M. abscessus* from hospital water distribution systems)

9

"Late" Bacterial Infections Following SOT

80% of Late Bacterial Infections are Community Acquired

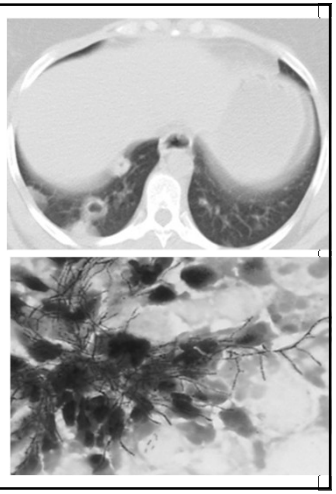
- *Streptococcus pneumoniae*
  - Incidence significantly > in SOT (146/100,000) vs general population (12/100,000)
  - Vaccination recommended
- *Listeria monocytogenes*
  - Bacteremia (Gram + Rods) / Diarrhea / Meningitis
  - Ampicillin treatment of choice
  - High relapse rate, treat for at least 3-6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

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

10

"Late" Bacterial Infections (Cont.)

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



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CMV Disease After SOT Indirect and Direct Effects

INDIRECT Effects:

- Acute and Chronic Rejection
- Opportunistic Super-Infections (Gram negative bacteria & Molds)

DIRECT Effects:

- CMV Syndrome – most common presentation
  - CMV in blood + fever + malaise, leukopenia, atypical lymphocytosis, thrombocytopenia
- Tissue Invasive Disease
  - Evidence of CMV on biopsy + compatible signs/symptoms

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Risk of CMV Disease After SOT

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

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

*Should receive leukocyte depleted blood products

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CMV Disease After SOT
Prophylactic Approaches

UNIVERSAL

All SOT recipients receive therapy during highest risk periods

- Expensive
- May induce resistance
- Some pts exposed unnecessarily

PREEMPTIVE

Treatment based on asymptomatic viral replication in blood

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

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

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CMV Prophylaxis After SOT

Bottomline:

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

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CMV Disease After SOT

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

16

CMV Disease After SOT
Ganciclovir Resistance

- **Suspect resistance if prolonged (> 6 weeks) (val)ganciclovir exposure AND:**
  - No reduction in viral load after 14 days of treatment
  - No clinical improvement after 14 days of treatment
- **Management of suspected ganciclovir resistance:**
  - Reduce immunosuppression
  - Switch to maribavir or foscarnet (± CMV hyperimmune globulin)

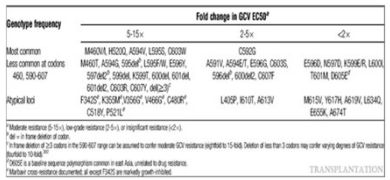
Lurain et al.JID 2002; Limaye et al Lancet 2000; Limaye et al JID 2002; Kotton et al Transplantation 2013.

17

CMV Disease After SOT
Antiviral Resistance

Key mutations have been associated with resistance

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



Genotype frequency	Fold change in GCV EC50*		
	5-15×	2-5×	<2×
Most common	M460I/I, H520Q, A594V, L595S, C603W		C592G
Less common at codons 460, 590-607	M460T, A594G, S595R[a], L595F/W, E596Y, 597del[b], 599ins, K599T, 600del, 601del, 601ins, 602del, C603R, C607Y, del≥3[c]	A591V, A594E/T, E596G, C603S, 596ins[a], 600ins[a], C607F	E596D, N597D, K599E/R, L600, T601M, D605E[a]
Atypical loci	F342S[a], K359M[a],V356G[a], V466G[a], C480R[a], C518Y, P521L[a]	L405P, I610T, A612V	M515V, Y617H, A619V, L634Q, E655K, A674T

* Moderate resistance (5-15×), low-grade resistance (2-5×), or insignificant resistance (<2×).
[a] del = in frame deletion of codon.
[b] In frame deletion of ≥3 codons in the 590-607 range can be assumed to confer moderate GCV resistance (eg,thibit to 15-fold). Deletion of less than 3 codons may confer varying degrees of GCV resistance (buried to 10-fold).[107]
[c] D605E is a baseline sequence polymorphism common in east Asia, unrelated to drug resistance.
[d] Marbavir cross-resistance documented, all except T347S are markedly growth-inhibited.

TRANSPLANTATION

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

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

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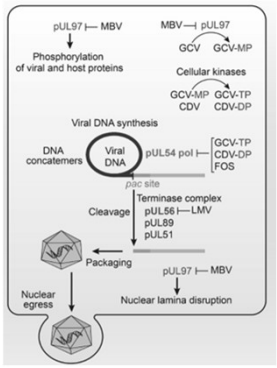
CMV Resistance: New Drug



Maribavir (MBV)

- Multi-modal CMV activity
  - Inhibits CMV DNA replication
  - Interferes with nuclear egress of viral capsid by inhibiting UL97 kinase
- UL97 kinase activates ganciclovir (GCV), thus MBV inhibits GCV activity
  - ⚠ MBV & GCV should not be used together
- MBV is active against many GCV resistant strains
  - Superior to SOC (Valgan/Gan, Foscarnet, or Cidofovir) in HSCT & SOT pts with refractory/resistant CMV infection
    - Cleared CMV viremia & resolved symptoms at 8 weeks
  - FDA approved Nov 2021 for "CMV (with or without genetic mutations that cause resistance) that does not respond to available antiviral treatment…"
  - ⚠ No activity against other herpes viruses (HSV/VZV)

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

19

Question #1

54-year-old male 60 days post-cardiac transplant was treated for rejection with steroids when fever and a non-tender anterior cervical mass appeared.

Biopsy showed nodal replacement by lymphocytes, many of which stained positively for Epstein-Barr virus as well as for the B cell marker, CD20.

His plasma EBV viral load was 10,000 copies /ml.

What is the most appropriate treatment for this condition?

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

20

Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

- Virus establishes latency in B-lymphocytes which serve as lifelong reservoirs
- EBV transformed B-lymphocytes give rise to PTLD (a few cases may arise from T-lymphocytes)
- Risk factors:
  - 1° EBV infection
  - Donor seropositive, Recipient seronegative
  - Anti-lymphocytic antibody therapy (T-cell depletion)
  - Organ transplanted (Intestine > Lung > Heart > Liver > Kidney)

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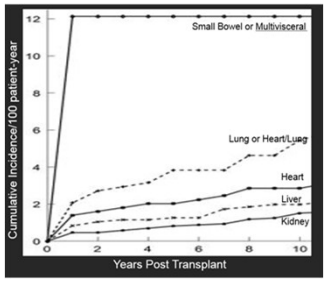
Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

- ~3% Cumulative 10-year incidence in SOT population
- Incidence varies based on organ transplanted
  - Small Bowel / Multivisceral – up to 32%
  - Lung / Heart / Liver - 3-12%
  - Kidney - 1-2%
- Biphasic pattern of disease after SOT:
  - First peak (20% cases) occurs 1st post-tx year
  - Second peak occurs 7-10 years post-tx



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

22

Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

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

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

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

23

Epstein Barr Virus: Post Transplant Lymphoproliferative Disorder (PTLD)

Treatment:

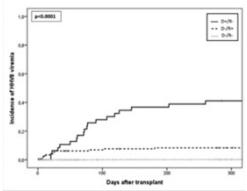
- Antivirals not effective on latently infected lymphocytes (antivirals only work in lytic phase)
- Reduce Immunosuppression (Response ~ 45%)
- Rituximab: Anti-CD20 monoclonal antibody (Response ~ 55%)
- Cytotoxic Combination (CHOP, ACVBP) Chemotherapy
  - Reserved for non-responsive disease
  - High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

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

24

HHV-8 After Solid Organ Transplant

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



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

25

HHV-8 Oncovirus Presentations

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

KICS could show up on the Boards!

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KICS: Working Definition

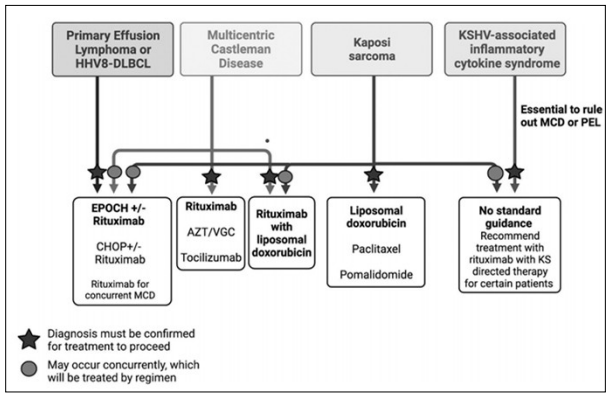
1. At least 2 **Clinical Manifestations** from at least 2 categories
   - **Symptoms**: Fever, Fatigue, Edema, Cachexia, Respiratory Symptoms, GI disturbance, Arthralgia/myalgia, Altered mental state, Neuropathy
   - **Laboratory**: Anemia, Thrombocytopenia, Hypoalbuminemia, Hyponatremia
   - **Radiographic**: Lymphadenopathy, Splenomegaly, Hepatomegaly, Body Cavity, Effusions
2. **Systemic Inflammation**: CRP (≥ 3g/dL)
3. **Elevated KSHV plasma viral load**: HHV-8 ≥ 1000 copies/mL
4. N**o pathologic evidence of MCD or PEL**
   (Requires biopsy of any lymphadenopathy if present)

Polizzotto, M. N., et al. Clinical Features and Outcomes of Patients With Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated Inflammation: Prospective Characterization of KSHV Inflammatory Cytokine Syndrome (KICS). *Clinical Infectious Diseases. 2016;62*(6):730–738.

27

Management of HHV8-Associated Diseases

- Consider KICS in SOT presenting with sepsis/multi-organ failure
- May be donor-derived or primary infection
- Management differs based on disease presentation



Patel R, Lurain K, Yarchoan R, Ramaswami R. Clinical management of Kaposi sarcoma herpesvirus-associated diseases: an update on disease manifestations and treatment strategies. Expert Rev Anti Infect Ther. 2023 Jul-Dec;21(9):929-941.

28

Question #2

- 52-year-old female S/P cadaveric renal transplant receiving tacrolimus, prednisone and mycophenolate
- Week 30 post transplant serum creatinine rose from 1.5 to 2.3 mg/dl
- Tacrolimus levels were in therapeutic range
- Urinalysis revealed one plus protein and no cells or casts

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Question #2

Which would be most helpful in understanding if BK virus was causing her renal failure?

A. Presence of decoy cells in urine cytology
B. Urine BK viral load
C. Urine culture for BK virus
D. Plasma BK viral load
E. Demonstration of BK inclusions in renal tubular epithelium on renal biopsy

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Polyomavirus
BK Virus Nephropathy

- Ubiquitous, DNA virus
  - 1° infxn – URI during early childhood
  - 80% worldwide population sero+
  - Renal & uroepithelial cells, site of latency
- Cause of nephropathy post renal transplant
  - Up to 15% of renal recipients effected
  - Time to onset 28-40 weeks (majority within 1st yr post tx)
  - Manifests as unexplained renal dysfunction (as does rejection)

Hayashi RY et al. UNOS Database; Abstract 76, 2006 World Transplant Congress; Ramos et al. *J Am Soc Nephrol* 2002;13:2145; Hirsch et al. Transplantation 2005;79:1277-1286

31

BK Virus Nephropathy
Diagnosis

- Replication in urine precedes replication in blood precedes nephropathy
- Renal Bx - "Gold Standard" for diagnosis
- Blood PCR
  - Sensitive (100%) but less specific (88%)
  - Cannot rule out rejection
  - Useful as indicator for biopsy
- Urine Cytology, Electron microscopy, & PCR
  - Detection in urine: Low PPV but High NPV

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

32

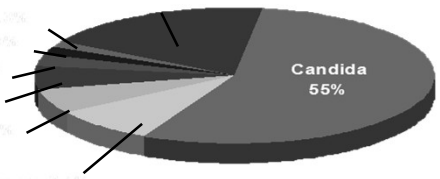
BK Virus Nephropathy Treatment

- Reduce immunosuppression
- Case series with variable success using:
  - Low-dose cidofovir
  - Leflunomide
- New drugs & randomized controlled trials needed
- Preemptive monitoring key to prevention

Hirsch et al. Transplantation 2005;79:1277-1286; Farasati et al. Transplantation 2004;79:116; Vats et al. Transplantation 2003;75:105; Kabambi et al. Am J Transplant 2003;3:186; Williams et al N Engl J Med 2005;352:1157-58.

33

Invasive Fungal Infections in Solid Organ Transplant Recipients



Type of fungal infection varies depending on organ transplanted

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

34

Invasive Fungal Infections According to Organ Transplanted

N=16,808

	Kidney	Heart	Pancreas	Liver	Lung	Small Bowel
12 Month IFI Incidence (%)	1.3	3.4	4.0	4.7	8.6	11.6
IFI Type (%)					70% Molds	
Candidiasis	49	49	76	68	23	85
Aspergillosis	14	23	5	11	44	0
Other molds	7	10	3	6	26	0
Cryptococcosis	15	10	5	6	2	5
Endemic	10	3	6	5	1	0
Pneumocystosis	1	3	1	0	2	0
Other	4	2	4	4	2	10

Pappas P, Alexander B, Andes D, et al. CID 2010:50:1101-1111

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Invasive Fungal Infections *Risk Factors After SOT*

Each solid organ group will have unique risks for IFIs

Strongly influenced by medical & surgical factors including technical complexity

Liver

- Re-transplantation
- Pre-tx fulminant hepatic or renal failure
- Heavy *Candida* colonization peri-tx
- Large volume intra-operative transfusions
- Bleeding complications requiring re-operation
- Choledochojejunostomy

CANDIDA

Lung

- Vulnerable anastomotic site
- Continuous environmental exposure
- *Aspergillus* colonization of airways
- CMV pneumonitis
- Acute rejection
- Obliterative bronchiolitis

ASPERGILLUS

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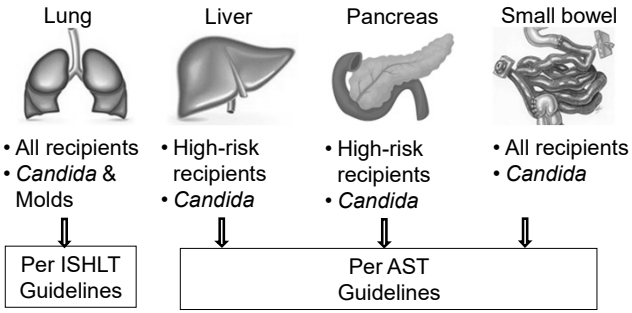
Antifungal Prophylaxis for Solid Organ Transplant Recipients



Husain S, et al. *J Heart Lung Transpl.* 2016;35:261-82.
Aslam S, Rotstein C. AST ID COP. *Am J Transpl.* 2019;33:e13623.
Husain S, Camargo J. AST ID COP. *Am J Transpl.* 2019;33:213544.

37

Tuberculosis

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

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Question #3

- 35-year-old female s/p heart transplant in France 90 days prior presented with fever, dyspnea and a diffuse pneumonia on chest CT.
- She was receiving prednisone, tacrolimus & mycophenolate.
- Both recipient & donor were CMV negative; she was not on CMV prophylaxis.
- She was on inhaled pentamidine for PCP prophylaxis.

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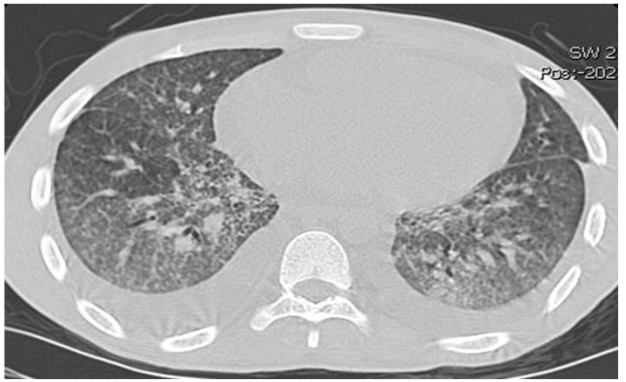
Question #3: Chest CT



40

Question #3

Trimethoprim-sulfamethoxazole was started empirically, and she began improving.

Bronchoalveolar lavage (BAL) was negative for:

- Pneumocystis by direct fluorescent antibody stain & PCR,
- Fungi by calcifour white / potassium hydroxide stain,
- Mycobacteria by AFB smear,
- Bacteria by gram stain, and
- Respiratory viruses by multiplex PCR

Routine bacterial BAL and blood cultures were negative.

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Question #3

Assuming trimethoprim-sulfamethoxazole was causing her improvement, which additional test on the BAL might have explained her improvement?

A. PCR for CMV
B. PCR for toxoplasmosis
C. PCR for tuberculosis
D. Galactomannan
E. Cold enrichment culture for Listeria

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Toxoplasmosis

- After SOT, acute toxoplasmosis can develop from reactivation, acquisition via blood transfusion or ingestion of contaminated food or water, or from the donated organ
- Donor seropositive/Recipient seronegative at high risk
- HEART > LIVER > KIDNEY TRANSPLANT
- Presents with myocarditis, pneumonitis & meningitis
- DIAGNOSIS:
  - PCR
  - Giemsa smear of BAL
  - Brain aspirate for tachyzoites
  - Immunoperoxidase stain of endocardial biopsy or other tissue
- TREATMENT: sulfadiazine-pyrimethamine-leucovorin

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Question #4

Liver transplant recipient on Bactrim & valganciclovir prophylaxis

presented 21 days post transplant with confusion, tremors, lethargy, anorexia

- Rapid progressive neurologic decline → agitation & delirium →intubation
- Brain MRI: non-revealing
- Blood & urine cultures: negative
- CSF: lymphocytic pleocytosis (25 WBCs/mm^3) & elevated protein
  - Gram stain, bacterial, fungal cultures negative for organisms
- Empiric intravenous ganciclovir, vancomycin, ceftriaxone & ampicillin
- Day 6 Repeat MRI: diffuse encephalitis
- Expired 13 days after neurologic symptom onset
- Donor was previously healthy presenting with subarachnoid hemorrhage
  - Toxicology screen: + cocaine & marijuana
  - Brain CT: expanding subarachnoid hemorrhage
  - Recently on camping trip

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Question #4

What is this presentation is most consistent with?

A. CMV encephalitis
B. HHV6 encephalitis
C. VZV encephalitis
D. Rabies encephalitis
E. Cryptococcal meningitis

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"Expected" Donor Derived Infections

- **Expected = known before tx or for which there are recognized standard prevention guidelines**
  - Cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - Toxoplasmosis

*United Network for Organ Sharing / Organ Procurement and Transplant Network

Ison M et al. Am J Transplant. 2009;9:1929-1935.

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"Unexpected" Donor Derived Infections

Viruses, Viruses, & Parasites, Oh My…

- Lymphocytic choriomeningitis virus (LCMV)
  - Hamsters and rodents
  - 4 outbreaks (3 USA, 1 Australia); 9 deaths

- Rabies virus
  - Unreported bat bite in donor
  - 3 outbreaks (2 USA, 1 Germany); 8 deaths

- Chagas' Disease (Trypanosoma cruzi)
  - Reduviid bug (Latin America)
  - Screening tests lack sensitivity
  - Multiple transmissions reported

- HIV, Hep C, Hep B, West Nile Virus (WNV)
  - Remember the "Window" prior to development of antibodies
  - Nucleic Acid Tests decrease "window" to ~5-10 days (HIV), 6-9 days (HCV)

Fisher SA et al. N Engl J Med. 2006;354:2235-2249. MMWR Morb Mortal Wkly Rep. 2008;57:799-801. Kusne S et al.Transpl. 2005;11:1295-1297. Maier T et al. CID 2010;50:1112-1119 Mattner F et al Infection. 2007;35(4):219-24. Grossi PA, et al. Am J Transpl. 2009;9:S19-S26.

47

Typical Presentations Of Unexpected Donor Derived Infections

- Most present in the first 3 months post transplant
- Look for epidemiologic clues for potential donor exposure in the stem (e.g. possible bat bites, new pet hamsters, tap water nasal irrigations, recent travel to a region endemic for certain pathogens)

PATHOGEN	PRESENTATION
LYMPHOCYTIC CHORIOMENINGITIS VIRUS	ENCEPHALITIS
RABIES	ENCEPHALITIS
TOXOPLASMOSIS	DIFFUSE PNEUMONIA MYOCARDITIS RETINITIS ENCEPHALITIS
WEST NILE VIRUS	MENINGITIS ENCEPHALITIS POLIOMYELITIS-LIKE FLACCID PARALYSIS
CHAGAS' DISEASE	FEVER MYOCARDITIS
ACANTHAMOEBA	SKIN LESION ENCEPHALITIS
BALAMUTHIA MANDRILLARIS	ENCEPHALITIS
VISCERAL LEISHMANIASIS	PANCYTOPENIA HEPATOSPLENOMEGALY
MALARIA	FEVER

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Vaccination Recommendations for SOT

Update vaccinations pre-SOT:

- COVID
- Hepatitis A, Hepatitis B, Flu, TDaP, Pneumococcal
- Live Varicella, MMR vaccines (≥4 wks pre-tx)
- HIB, Meningococcal if planned splenectomy (e.g. Multivisceral Tx)

Recommended post-SOT:

(Delay 1 month post-tx; 3–6 months to maximize response)

- COVID
- Pneumococcal
- Tetanus-diphtheria toxoid
- Inactivated Influenza

Live vaccines are NOT recommended after SOT including:

- Measles Mumps Rubella
- Varicella
- Inhaled influenza
- Oral polio
- Yellow fever
- BCG
- Small pox
- Salmonella typhi (oral)

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Solid Organ Transplant
Patient Travel

- **REGIONAL EXPOSURES**
  - **COCCIDIOIDOMYCOSIS: Southwest U.S.**
  - **HISTOPLASMOSIS: Central/Mid-Atlantic U.S.**
  - **VISCERAL LEISHMANIASIS: Spain, Mediterranean Basin**
  - **MALARIA: Tropics**
  - **BABESIA MICROTI: Northeast & Upper Midwest U.S.**
- **AND ALL THE "NORMAL" RISKS TO TRAVELERS**
  - **DIARRHEA**
  - **STIs**
  - **MDR-TB**
  - **BLOOD SUPPLY (need for TRANSFUSIONS), etc…**
- **AVOID LIVE VACCINES: Yellow Fever, Oral typhoid, etc.**
- **DRUG INTERACTIONS →Transplant meds + travel related prophylactic agents**

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Key Drug Toxicities / Syndromes

- Calcineurin inhibitors and TTP and PRES (RPLS)
- Sirolimus-induced pneumonitis
  - Progressive interstitial pneumonitis (22% in one study)
  - Risk factors: late switch to sirolimus & impaired renal function
  - Symptoms: dyspnea, dry cough, fever, and fatigue
    - Radiographic & bronchoalveolar lavage consistent with bronchiolitis obliterans organizing pneumonia & lymphocytic alveolitis
  - Recovery with sirolimus withdrawal

Euvrard S et al. N Engl J Med. 2012;367(4):329. Champion L et al. Ann Intern Med 2006;144:505.
Weiner SM et al. Nephrol Dial Transplant. 2007;22(12):3631.

51

Other Pearls for Boards…

If you're thinking PCP but its not → think TOXO

Patient presenting atypically during first month post transplant → think donor transmitted infection

- Rabies, WNV, Coccidioides, Chagas, LCMV (look for epidemiologic clues in stem)

Remember drug interactions and syndromes

- Addition of mold active azole leading to acute kidney injury from elevated CNI
- TTP and PRES induced by calcineurin inhibitors
- Sirolimus-induced pneumonitis

Remember *Strongyloides* hyperinfection syndrome

TB- Don't miss a case!

BKV, CMV and EBV/PTLD – know how to diagnose and manage

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Thank You!

barbara.alexander@duke.edu

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Wednesday, August 20, 2025

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Core Concepts: Antifungal Drugs

Barbara Alexander, MD

Antifungal Drugs

Barbara D. Alexander, MD, MHS, FIDSA
Vice-Chief, Transplant Infectious Diseases Service
Head, Clinical Mycology Laboratory
Director, Transplant Infectious Diseases Fellowship Program
Professor of Medicine and Pathology
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7/22/2025

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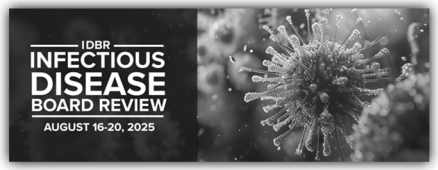


Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant:** Scynexis, GSK, Astellas, Pulmocide, HealthTrackRx, Basilea, TFF Pharma
- **Research Grant to My Institution:** Karius
- **Clinical Trials (Site PI/Study PI):** Scynexis, F2G
- **Royalties (Chapter Author):** UpToDate

2

Agenda

1. Review of Antifungals
2. Questions on antifungals with answers
3. New stuff (not on boards)

3

Antifungal Drugs

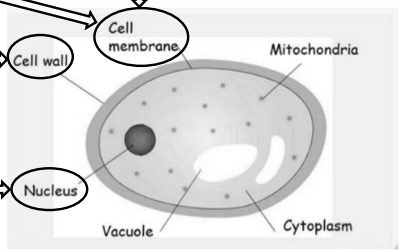
Four Main Drug Classes

Azoles stop ergosterol synthesis for cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Pyrimidines (Flucytosine) blocks DNA synthesis in nucleus

Polyenes (Amphotericin B) makes cell membrane leak



4

Reasons for Treatment Failure

- **"Clinical"**

  Host defense inadequate
  - Underlying disease uncontrolled
  - Persistent neutropenia / Immunosuppressive drug use

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

- **"Microbiologic"**

  Microbial resistance
  - Intrinsic - present for all members of the species despite lack of exposure to a drug
  - Acquired - develops *after* exposure to a drug

5

Antifungal Resistance
Altered Target Enzymes

AZOLE RESISTANCE IN CANDIDA and ASPERGILLUS
- Fungus modifies the drug target: 14-α-sterol demethylase
  - Changes in ERG11 gene (yeasts), cyp51A gene (molds)
- Azoles no longer block synthesis of ergosterol, which is necessary for cytoplasmic membrane function
- Cross resistance varies with azole

ECHINOCANDIN RESISTANCE IN CANDIDA
- Fungus modifies the drug targets: glucan synthase
  - Alterations in FKS1 & FKS2 genes
- Echinocandins no longer block synthesis of beta-D-glucan, which is necessary for cell wall synthesis
- Cross resistance between echinocandins is usual

6

Antifungal Resistant Species

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

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

7

Amphotericin B

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

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Azoles

ALL AZOLES ARE TERATOGENIC; CYP3A4 DRUG INTERACTIONS

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

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Fluconazole THE FUNDAMENTALS

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

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Voriconazole THE FUNDAMENTALS

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

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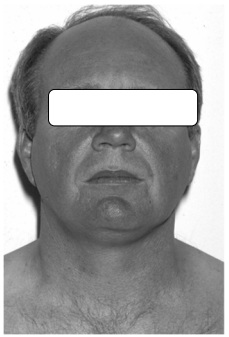
Voriconazole Side Effects

Photosensitivity

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



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

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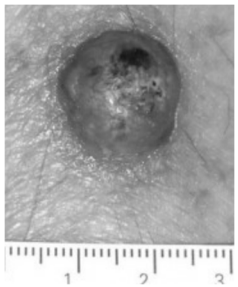
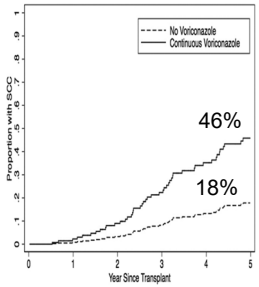
Voriconazole Side Effects
Skin Cancer





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

Voriconazole Prophylaxis

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

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

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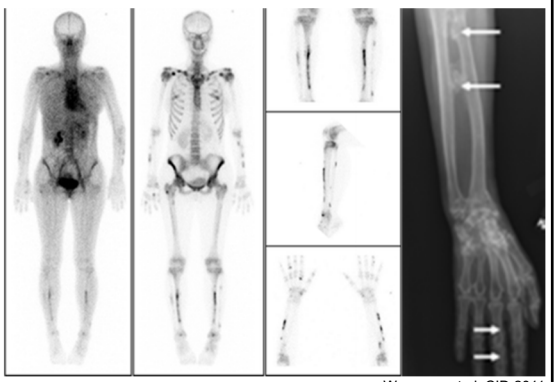
Voriconazole Side Effects

Periostitis:

- Months of Rx
- Bone pain
- Alk phos high
- Plasma fluoride high (fluorosis)
- Bone scan / Xrays
- Exostoses



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

14

Posaconazole THE FUNDAMENTALS

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

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Isavuconazole THE FUNDAMENTALS

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

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Echinocandins

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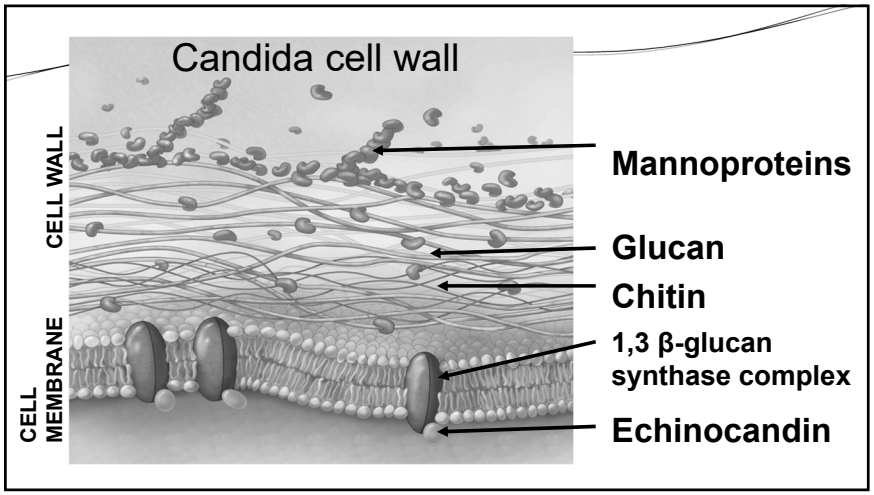

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Caspofungin, Micafungin, Anidulafungin, Rezafungin

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

19

Flucytosine

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

20

Now for a few questions

21

Question #1

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

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

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

22

Question #2

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

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

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

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

23

Question #3

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

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

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Question #4

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

Which of the following would be most appropriate?

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

25

Question #5

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

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

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

26

Question #6

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

What was the most probable cause?

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

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Question #7

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

Which of the following would be preferred?

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

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Question #8

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

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

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

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

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

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Take Home Messages…

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

30

Take Home, continued…

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

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New Oral Antifungals Approved for Vulvovaginal Candidiasis

Ibrexafungerp – novel ORAL glucan synthase inhibitor (triterpenoid)

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

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

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

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Investigational Antifungals in Clinical Trials

- **Olorofim**. Novel drug for *Aspergillus, Coccidioides*, some molds including *Scedosporium, Lomentospora* (not Mucorales or yeast). PO, ALT rises in 8%
- **Fosmanogepix**. In vitro activity against *Candida* (not *C.krusei*), *Aspergillus, Fusarium, Scedosporium*, (not Mucorales). PO, IV.
- **Encochleated amphotericin B**: PO. low absorption.
- **Opelconazole**: aerosol for chronic aspergillosis

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Thank You

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Wednesday, August 20, 2025

53

Penicillin Allergies

Sandra Nelson, MD

Penicillin Allergy

Sandra B. Nelson, MD

Massachusetts General Hospital
Harvard Medical School

7/22/2025

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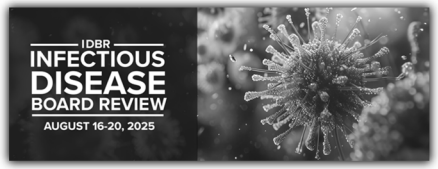

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Question #1

A 73-year-old woman undergoing chemotherapy for cholangiocarcinoma is hospitalized for bacteremia and sepsis due to ampicillin-susceptible *Enterococcus faecalis*. She is currently receiving IV vancomycin but has had progressive renal injury. She has a history of allergy to amoxicillin that is listed in the records as rash; the family recalls that she went to the ED when the rash occurred several years earlier. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available.

3

3

Question #1

You are asked about optimal antibiotic treatment.

What do you advise?

A. Administer IV ampicillin without prior testing
B. Skin test for penicillin reaction; if negative then administer full dose ampicillin
C. Skin test for penicillin reaction; if negative then administer test dose ampicillin followed by full dose ampicillin
D. Desensitize to ampicillin
E. Continue vancomycin; there is no safe path for transition to ampicillin

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53 Penicillin Allergies
Speaker: Sandra Nelson, MD

Penicillin (PCN) Allergy: Premise

- 10% of the US population have reported penicillin allergy
- Majority with history of PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Some reactions are not allergic
  - Allergic reactions do not always recur
  - Allergies often wane with time

- PCN allergy is associated with important morbidity
  - Higher risk of MRSA and VRE, *C difficile* colitis, surgical site infection
  - Greater associated antimicrobial costs and toxicities

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Likelihood of True Penicillin Allergy

- Positive skin test most likely with:
  - **F** ive or fewer years since the reaction
  - **A** naphylaxis or angioedema
  - **S** evere cutaneous adverse reaction
  - **T** reatment required for reaction

PEN-FAST Tool

Questions

1. **PEN - Penicillin allergy reported by patient**
2. F - Five years or less since reaction
3. A - Anaphylaxis or angioedema
4. S - Severe cutaneous adverse reaction
5. T - Treatment required for reaction

About

The PEN-FAST penicillin allergy clinical decision rule enables point-of-care risk assessment of patient-reported penicillin allergies. It requires three clinical criteria:

- Time (five years or less) from penicillin allergy episode (2 points)
- Phenotype (anaphylaxis/angioedema OR SCAR) (2 points)
- Treatment required for penicillin allergy episode (1 point)

The risk of a positive penicillin allergy test can be accurately predicted from these criteria:

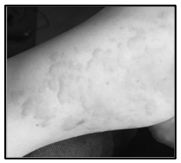
- 0 points – Very low risk of positive penicillin allergy test <1%
- 1-2 points – Low risk of positive penicillin allergy test 5%
- 3 points – Moderate risk of positive penicillin allergy test 20%
- 4 points – High risk of positive penicillin allergy test 50%

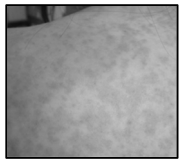
PEN-FAST Decision Tool: https://qxmd.com/calculate/calculator_752/pen-fast-penicillin-allergy-risk-tool 6

6

Deciphering Cutaneous Reactions

- IgE Mediated Reactions (hives)
  - Occur within minutes to hours, resolve within 24 hours
  - Often recurs with repeat exposure
- Benign T-cell mediated
  - Morbilliform or maculopapular
  - May have associated eosinophilia
  - Usual onset days to weeks
  - Persists longer than 24 hours and resolves over days to weeks
  - May not recur with subsequent exposure
  - Can ”treat through” with monitoring if drug essential





Shenoy JAMA 2019;321:188 7

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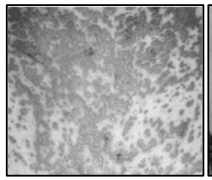
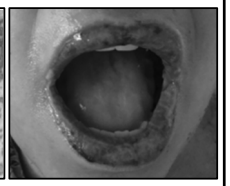
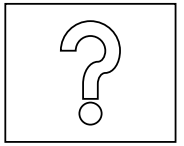
Deciphering Cutaneous Reactions

- Severe cutaneous reactions
  - DRESS, AGEP and SJS/TEN
  - Usual onset days to weeks
  - Blistering, mucosal involvement, severe skin desquamation, organ involvement





- Vague or unknown skin reaction
  - Evaluate risk of severe cutaneous reaction
  - Assume possibly IgE mediated



DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms
AGEP: Acute Generalized Exanthematous Pustulosis
SJS: Stevens-Johnson Syndrome
TEN: Toxic Epidermal Necrolysis
Shenoy JAMA 2019;321:188
Stern NEJM 2012;366:2492 8

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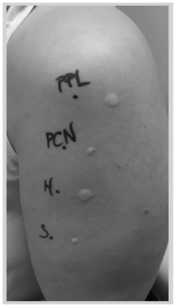
53 Penicillin Allergies
Speaker: Sandra Nelson, MD

Options for Approaching PCN Allergy

1. Monitored oral challenge
   - Use with low-risk reactions (e.g., remote rash)
2. Penicillin skin testing
   - Procedure: percutaneous and intradermal administration of PPL (Pre-Pen®) and penicillin G (minor antigen)
   - Use with history of or suspected IgE mediated reaction
   - Consider for unknown history when other high-risk features
   - If negative, followed by test dose of amoxicillin or of implicated or desired drug



Positive Intradermal Test

PPL: penicilloyl polylysine Shenoy JAMA 2019;321:188 9

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Options for Approaching PCN Allergy

3. Graded challenge (also called test dose procedure)
   - Procedure: 1/4th to 1/10th dose, followed by full dose 30-60 minutes later
   - Can be used as a first step if suspicion for immediate reaction is low
   - Also used after negative PCN skin testing
4. Desensitization
   - Administration of increasing doses every 15-30 minutes until therapeutic dose reached
   - Used for positive skin test and/or confirmed immediate reaction when a penicillin is the best therapy for an important infection
   - Desensitization wanes with missed doses (3 half-lives)
5. Use of alternate therapy

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Putting it All Together: Penicillin Skin Reactions

IgE Mediated (Urticaria)	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug
Benign Skin Rash	If a penicillin: amoxicillin oral challenge Any cephalosporin safe
Severe Cutaneous Adverse Reaction SJS/TEN, DRESS, AGEP	Avoid beta-lactams

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What About Non-cutaneous Reactions?

IgE Mediated Angioedema and Anaphylaxis	Penicillin Skin testing If positive: desensitization or alternative therapy If negative: test dose amoxicillin or desired drug
Antibody mediated (*Hemolytic anemia, neutropenia, thrombocytopenia*) Immune-complex (*vasculitis, serum sickness*) Cell-mediated (*Interstitial nephritis, drug-induced liver injury*)	No available testing In general, when severe avoid beta-lactams

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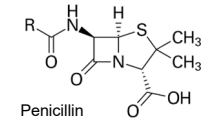
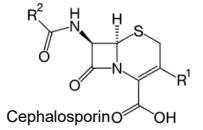
PCN Allergy and Use of Cephalosporins

- Significant cross reactivity rare
  - higher with earlier generation cephalosporins
- For IgE mediated PCN allergy:
  - use structurally dissimilar cephalosporin (e.g. all 3rd/4th generation; cefazolin) without prior testing
  - use structurally similar (most 1st/2nd gen) after PCN skin testing and amoxicillin challenge
- Mild delayed drug rash:
  - any cephalosporin OK
- Avoid if severe reaction to PCN





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Question #2

A 43-year-old man with diabetes is hospitalized with a closed tibial fracture. Three years ago, when he was being treated for a foot infection with cefepime he developed a very itchy rash after several weeks of treatment. The anesthesiologist calls to ask advice about surgical antibiotic prophylaxis prior to operative fixation.

14

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Question #2

What do you do counsel?

A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin

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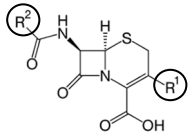
Cephalosporin Allergy



- Allergy often arises from side chains
  - More common than beta-lactam ring
- Probability of reaction higher when cephalosporins with similar side chains used (R1 > R2)
- Side chain tables are available to guide cross-reactivity

Similar Side Chain Groups (R1)
Amoxicillin, Cefadroxil, Cefprozil
Ampicillin, Cefaclor, Cephalexin
Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime
Ceftazidime, Cefiderocol, Aztreonam

https://adsp.nm.org/allergy-resources.html

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53 Penicillin Allergies
Speaker: Sandra Nelson, MD

A Few More Testable Points

- Selective allergy to the aminopenicillins occurs
  - A patient that tolerates PCN may still be allergic to aminopenicillins
  - A patient that tolerates aminopenicillins is not allergic to PCN
- Cefazolin has different side chains from all other cephalosporins
  - Can be administered in patients with IgE mediated reaction to penicillins
- Ceftazidime does not share side chains with ceftriaxone or cefepime
- Aztreonam can be safely used in individuals with beta-lactam allergy except for those allergic to ceftazidime or cefiderocol

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Thank you and good luck!

"The penicillin looks good."

18

18

Wednesday, August 20, 2025

54

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey Rose, MD

Kitchen Sink: Syndromes Not Covered Elsewhere

Stacey R. Rose, MD

Associate Professor of Medicine, Infectious Diseases
Associate Director, Center for Professionalism
Baylor College of Medicine

7/25/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Session Plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)

3

3

Question #1

- A 51-year-old male with past medical history significant for insulin dependent diabetes presents with a six-month history of progressive arthralgias, abdominal pain, diarrhea, weight loss, and low-grade fevers.
- Work up thus far:
  - Negative blood cultures x 2
  - Negative Rheumatoid factor
  - Normal metabolic panels
  - Mild normocytic anemia

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54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Question #1

Which of the following tests will most likely yield the diagnosis?

A. Anti-streptolysin O Antibody
B. Anti-nuclear Antibody
C. Stool ova and parasite
D. Duodenal biopsy

5

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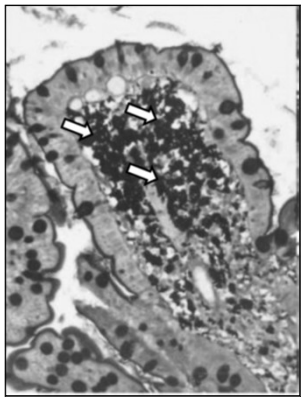
Whipple's Disease

- Caused by *Trophyrema whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle aged, Caucasian men
- Diagnosis often delayed due to indolent clinical presentation
- Most commonly diagnosed via duodenal biopsy, stained with PAS
- PCR increasingly used



Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows).

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555.

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Whipple's: Clinical Presentations

TABLE 1 Clinical manifestations of *Tropheryma whipplei* infection[a]

Classic Whipple's disease (% incidence)	Chronic localized infections[b]	Acute infections[b]
Weight loss (79–99)	Endocarditis	Gastroenteritis
Gastroenteritis (63–85)	Encephalitis	Pneumonia
Abdominal pain (23–60)		Bacteremia
Arthritis (20–83)		
Neurological symptoms (6–63)		

Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. 2017. Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 30:529 –555.

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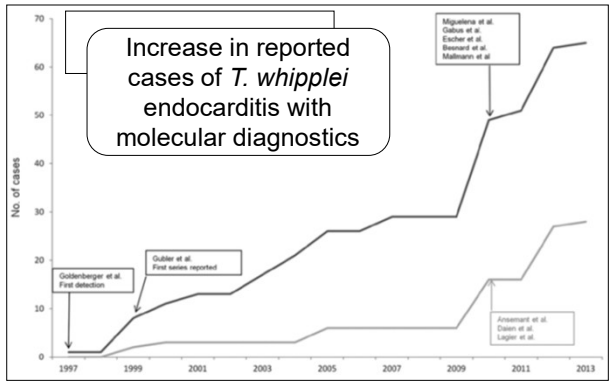
Whipple's Endocarditis – Increasingly Diagnosed



- Consider in patients with arthralgias plus "culture negative" endocarditis
- *T. whipplei* PCR from blood added to Duke's criteria (2023) for diagnosis of endocarditis

Fenollar F, Célard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. Tropheryma whipplei endocarditis. *Emerg Infect Dis*. 2013
Fowler VG, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. *Clin Infect Dis*. 2023

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54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Whipple's: Treatment

No gold standard

Options:

- Ceftriaxone or meropenem plus prolonged trimethoprim-sulfamethoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

Symptoms improve, but relapse is common without prolonged treatment / suppression

Clinical manifestations, treatment, and diagnosis of Tropheryma whipplei infections. Clin Microbiol Rev 2017.
Whipple's disease and Tropheryma whipplei infections: from bench to bedside. Lancet Infect Dis. 2022
Principles and Practice of Infectious Diseases, 9th ed

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- Cause: *Trophyrema Whipplei*
- Epidemiology: middle aged, Caucasian males
- Clinical presentation: classic – *arthralgia, diarrhea, weight loss*
- Localized infection e.g., *endocarditis* (increasingly recognized)
- Diagnosis with *duodenal biopsy* (*PAS* stain; foamy macrophages)
  or *PCR* of infected tissue or blood
- Prolonged treatment needed to prevent relapse

Whipple's Disease

Take Home Points

10

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Question #2

- A 20-year-old female schoolteacher presents with a 1-week history of fever and pain / swelling in knees, elbows and wrists. She notes that the pain moves from joint to joint.
- She reports being ill ~3 weeks prior with sore throat and headache which resolved without specific treatment.
- She has no rash or lymphadenopathy.
- She denies travel. She is sexually active with one male partner, using barrier protection (condoms).
- Labs are notable for elevated ESR and CRP and + ASO and Anti-DNase B titers; pregnancy and HIV tests (4th generation Ag/Ab) are negative.

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Question #2

Which of the following is the best explanation for her symptoms?

A. Acute HIV infection
B. Mononucleosis due to Epstein Barr Virus
C. Acute rheumatic fever
D. Lemierre's syndrome

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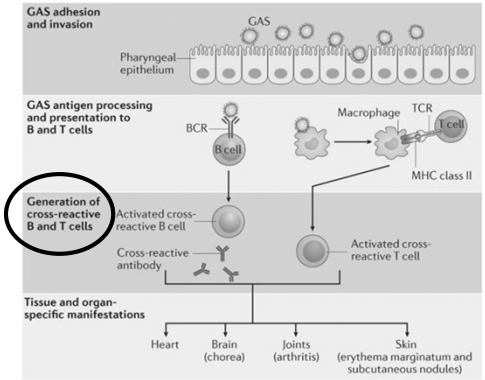
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Acute Rheumatic Fever



- Rare in US (0.5 per 100K per year), but common worldwide (0.5 million per year)
- Affects ***children / young adults***
- Recurrence common
- *Pathogenesis*: immune response following *Streptococcus pyogenes* infection (pharyngitis; impetigo)
- Leads to systemic manifestations (**arthritis**, **carditis**, **chorea**, **skin**)

Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers*. 2016

13

13

Revised Jones Criteria

For patients with evidence of prior GAS infection*,

Acute Rheumatic fever =

2 MAJOR

OR

1 MAJOR plus 2 MINOR

Major	Minor
Arthritis (usually migratory polyarthritis)	Arthralgia
Carditis (clinical or subclinical)	Fever
Chorea	Elevated ESR or CRP
Erythema marginatum	Prolonged PR interval (unless carditis is a major criterion)
Subcutaneous nodules	

*e.g., rapid strep test; culture; anti-streptolysin-O titer (ASO) or anti-DNase B (ADB)

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015

14

14

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*e.g., rapid strep test; culture; anti-streptolysin-O titer (ASO) or anti-DNase B (ADB)

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015

15

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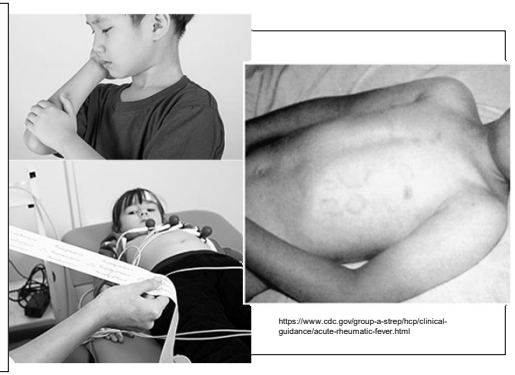
Recognizing Acute Rheumatic Fever

- **Timing**: ~19 d after GAS infection
- **Arthritis**: migratory, polyarthritis involving large joints (knees, ankles, elbows, wrists)
- **Carditis**: wide range of effects – e.g. pericarditis, systolic dysfunction, valvular disease
- **Chorea**: late manifestation; involuntary movements
- **Skin**: Subcutaneous nodules; erythema marginatum (blanches; transient) – rare but specific



https://www.cdc.gov/group-a-strep/hcp/clinical-guidance/acute-rheumatic-fever.html

Karthikeyan G, Guilherme L. Acute rheumatic fever. *Lancet*. 2018.
Principles and Practice of Infectious Disease, 9th ed.

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54 Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Treatment and Prophylaxis of Acute Rheumatic Fever

Primary Episode	Secondary Prophylaxis
IM benzathine penicillin x 1 or Oral penicillin x 10 d	IM benzathine penicillin q 4 weeks

Goal: *to prevent rheumatic heart disease*

Duration of ppx: *varies by severity of primary illness*

Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap: A Scientific Statement From the American Heart Association. *Circulation*. 2020
Principles and Practice of Infectious Diseases, 9th ed.

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CATEGORY	DURATION AFTER LAST ATTACK
Rheumatic fever with carditis and residual heart disease (persistent valvular disease[a])	10 yr or until age 40 yr, whichever is longer; sometimes lifelong prophylaxis (see text)
Rheumatic fever with carditis but no residual heart disease (no valvular disease[a])	10 yr or until age 21 yr, whichever is longer
Rheumatic fever without carditis	5 yr or until age 21 yr, whichever is longer

Duration of Secondary Prophylaxis Following Acute Rheumatic Fever:
Longest if Carditis and Residual Valvular Disease

Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap: A Scientific Statement From the American Heart Association. *Circulation*. 2020
Principles and Practice of Infectious Diseases, 9th ed.

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- Cause: immune dysregulation following *S. pyogenes* infection
- Epidemiology: children / young adults; rare in US
- Clinical presentation: ~3 weeks following GAS infection
  - Major: *migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum*
  - Minor: *fever, arthralgia, elevated ESR/CRP; PR prolongation*
- Diagnosis based on Jones criteria = 2 major OR 1 major + 2 minor (plus e/o prior GAS infection e.g. ASO titer)
- Treatment and secondary ppx with IM Penicillin; duration based on carditis (10 yr or to age 40 if carditis + residual valvular disease)

Acute Rheumatic Fever

Take Home Points

19

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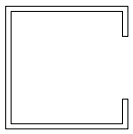
Question #3



- A 34-year-old male with a history of injection drug use presents to the emergency room with two days of blurry vision and difficulty swallowing. He is also beginning to feel weak in his arm muscles.
- On examination, vital signs are normal, but the patient is noted to have ptosis and sluggish pupillary responses as well as slurred speech.

20

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Question #3

Which of the following treatments are recommended?

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin

C

21

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Botulism

https://phil.cdc.gov/details.aspx?pid=2107

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Toxins prevent release of acetylcholine in neuromuscular junction
- Leads to flaccid paralysis of motor and autonomic nerves, beginning with the cranial nerves (*descending* weakness)
- DX: culture or detection of toxin

**other neurotoxin producing species of Clostridium:*
C. butyricum, or *C. baratii*

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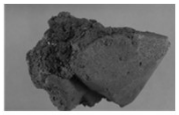
Botulism

Bioterrorism Potential (Aerosolization)

Foodborne

Infant



Wound (black-tar heroin)

Iatrogenic

Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR 2019.
https://www.cdc.gov/botulism/hcp/clinical-overview/index.html; *Principles and Practice of Infectious Diseases, 9th ed.*

23

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RED FLAGS: symmetric CN palsies and descending / symmetric flaccid paralysis should raise suspicion for botulism

Adverse Effects Linked to Counterfeit or Mishandled Botulinum Toxin Injections

Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
April 23 2024, 11:00 AM ET
CDCHAN-00507

https://emergency.cdc.gov/han/2024/han00507.asp

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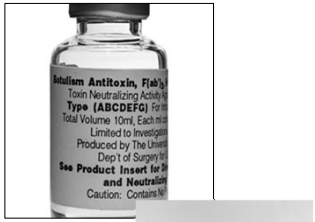
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Botulism Treatment

Supportive Care	Antitoxin
• Ventilatory support for respiratory compromise • Wound debridement	• Administer Botulinum anti-toxin (BAT) asap to prevent progression • For infant botulism syndrome, use Botulinum immune globulin (BabyBIG®)



Rao AK, Sobel J, Chatham-Stephens K, Luquez C. Clinical Guidelines for Diagnosis and Treatment of Botulism, 2021. *MMWR Recomm Rep.* 2021.
Principles and Practice of Infectious Diseases, 9th ed.; https://www.cdc.gov/botulism/hcp/clinician-resources/index.html

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- Cause: *Clostridium botulinum* toxin impedes acetylcholine release from neuromuscular junction
- Epidemiology: food-borne (home-canned veggies, fruits, fish); infant (honey); wound (black-tar heroin); iatrogenic (rare)
- Clinical features: *symmetric, descending flaccid paralysis*, starting with *cranial nerves* (ptosis, blurry vision, slurred speech)
- Diagnosis: clinical; confirmed by culture or detection of toxin
- Treatment: *antitoxin* & supportive care; wound debridement

Botulism

Take Home Points

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Question #4

- A 23-year-old female presents with a non-productive cough for 2 weeks. She describes spells during which she coughs repeatedly for several minutes. On two occasions she vomited after coughing.
- She reports episodes of sweating but has had no fever or other constitutional symptoms.
- She has tried several cough medicines, but nothing seems to help.
- PCR respiratory panel was positive for *Bordatella pertussis*.
- She works as a nurse in a pediatric intensive care unit and would like guidance for when she can return to work.

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Question #4

https://www.youtube.com/watch?v=31tnXPlhA7w (NEJMvideo)

Which of the following would you recommend for this patient?

A. Azithromycin, with return to work after 5 days
B. Azithromycin, with return to work after first dose
C. No treatment, with return to work after 5 days
D. No treatment; can return to work immediately

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54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Whooping cough cases surge as vaccine rates fall

The U.S. has tallied 8,077 cases of whooping cough in 2025, compared with 3,847 cases in the same period last year, federal data shows.

April 22, 2025

5 min

An infant receives a vaccination in Fayetteville, Georgia, in 2021. (Angie Wang/AP)

https://www.washingtonpost.com/health/2025/04/22/whooping-cough-pertussis-cases-rise/ 29

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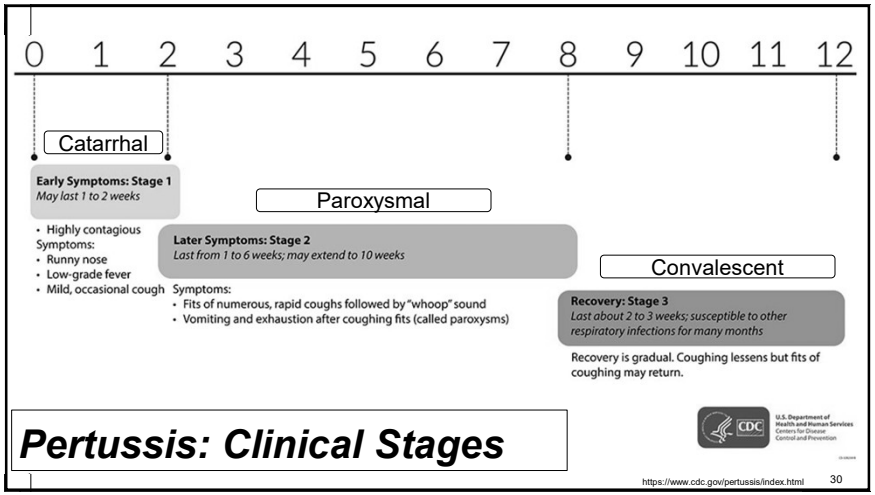

Pertussis: Clinical Stages

https://www.cdc.gov/pertussis/index.html 30

30

Pertussis Diagnosis – Requires Clinical Suspicion

Clinical case criteria (in absence of alternate dx):

- Cough illness lasting ≥2 weeks, with at least one of the following:
  - Paroxysms of coughing; **OR**
  - Inspiratory whoop; **OR**
  - Post-tussive vomiting; **OR**
  - Apnea (with or without cyanosis)

Polymerase chain reaction (PCR) is most sensitive and specific

- Nasopharyngeal swab / aspirate
- Best if sent within first 3 weeks of illness

https://ndc.services.cdc.gov/case-definitions/pertussis-2020/ https://www.cdc.gov/pertussis/php/pcr-bestpractices/?CDC_AAref_Val=https://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-pcr-bestpractices.html
Clinical evaluation and validation of laboratory methods for the diagnosis of Bordetella pertussis infection: Culture, polymerase chain reaction (PCR) and anti-pertussis toxin IgG serology (IgG-PT). *PLoS One*. 2018;
Evaluation of BioFire Respiratory Panel 2 plus for Detection of Bordetella pertussis in Nasopharyngeal Swab Specimens from Children with Clinically Suspected Pertussis. Microbiol Spectr. 2023

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Treatment and Post Exposure Prophylaxis

- TREAT with macrolide (e.g. azithromycin) if within 3 weeks of onset
- Treat within 6 weeks of onset for infants or pregnant women

- POST EXPOSURE PROPHYLAXIS (PEP) given to household members and contacts at risk of severe infection (within 3 weeks of exposure)

https://www.cdc.gov/pertussis/index.html
Decker MD, Edwards KM. Pertussis (Whooping Cough). *J Infect Dis*. 2021.

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54 Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Pertussis: Recommendations for Health Care Workers (HCW)

Symptomatic infection: exclude from work for 21 days from onset of cough OR until 5 days after the start of effective antimicrobial therapy

Exposure: regardless of vaccination status, administer post-exposure prophylaxis OR exclude from work for 21 days (if HCW interacts with persons at increased risk of complications)

Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC Guidelines. *MMWR Recomm Rep*. 2005.
https://www.cdc.gov/infection-control/hcp/healthcare-personnel-epidemiology-control/pertussis.html

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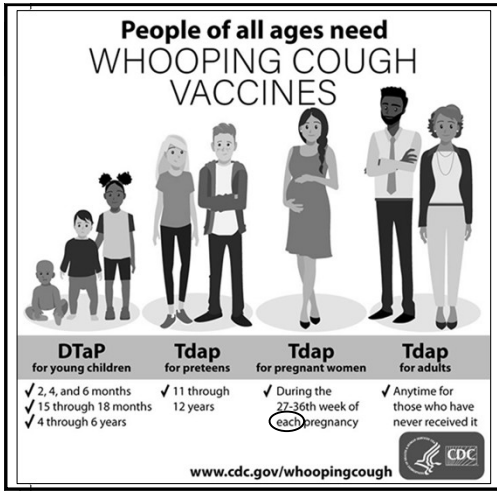

Pertussis Vaccination

https://www.cdc.gov/pertussis/vaccines/index.html

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- Epidemiology: infants > adolescents
- *High risk for severe disease: infants, pregnant women*, lung disease
- Clinical presentation: *cough* lasting 2+ weeks plus *paroxysmal cough*, *inspiratory whoop*, *post-tussive vomiting or apnea*
- Diagnosis: clinical; PCR
- Treat with *macrolide within 3 wks* of onset (6 wks if high risk)
- Post-exposure prophylaxis: (within 3 wks of exposure) for *household contacts* / *high risk* / *HCW* likely to interact with high-risk patients
- Symptomatic HCW can return to work after 5 d of effective treatment or 21 d after cough onset

Bordetella pertussis

Take Home Points

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Question #5

- A 34-year-old motorcyclist is involved in a severe motor vehicle accident, resulting in laceration of the spleen and requiring splenectomy.

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Question #5

Post-splenectomy, the patient is at increased risk of severe disease due to which of the following microorganisms?

A. Helicobacter pylori
B. Capnocytophaga canimorsus
C. Candida glabrata
D. Clostridium difficile

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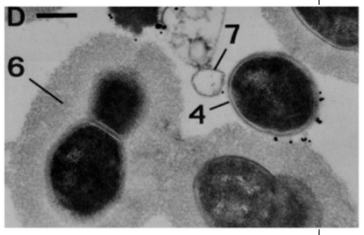
Splenectomy and Infection Risk



Skov Sørensen et al. (1988) Infect Immun 56: 1890-1896

Why: reduced clearance of encapsulated organisms; impaired humoral immunity

On the boards, look for…
- *Streptococcus pneumonia*
- *Hemophilus influenza type B*
- *Neisseria meningitidis*
- *Capnocytophaga canimorsus (dog bite)*
- *Babesia microti (tick borne)*
- *Bordetella holmesii*
- *Salmonella typhi*

Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014

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Strategies to Reduce Infection Risk in Asplenia

Vaccination for Encapsulated Organisms
- Pneumococcus
- Meningococcus
- Hemophilus Influenza Type B

Penicillin Prophylaxis
- Children < 5 years
- Older children/ adults within 1-2 years of splenectomy
- Any age: secondary prevention (lifelong) following sepsis

Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014; Lee GM. Preventing infections in children and adults with asplenia. Hematology Am Soc Hematol Educ Program. 2020

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- Increased risk for infection with encapsulated organisms (and others)…
  - *S. pneumoniae; N. meningitidis; HIB; Capnocytophaga; Babesia; Salmonella typhi*
- Reduce risk of infection via:
  - Immunizations
  - PCN ppx if < 5 yrs old; recent splenectomy; h/o sepsis

Infection in Asplenia

Take Home Points

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Question #6

- A 19-year-old male with no past medical history presents with acute onset of pain that started in the periumbilical region and moved to the lower region.
- Physical exam is notable for point tenderness in the right lower quadrant.
- Appendicitis is diagnosed based on clinical findings and imaging results, with no evidence of periappendiceal abscess.
- The patient wants to avoid surgery if at all possible.

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Question #6

You note that antibiotic therapy for uncomplicated appendicitis has become accepted practice by some physicians and offer to counsel him regarding risks and benefits.

Which of the following is a recognized disadvantage of this approach, when compared to immediate surgery?

A. Risk of *C. difficile* within 30 days
B. Risk of bowel obstruction in 1 year
C. 20% risk of intra-abdominal abscess within 30 days
D. 30-50% risk of subsequent appendectomy within 4 years

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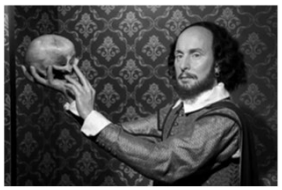
Appendicitis: to cut or not to cut…



In several studies, non-operative management (antibiotics alone) was "non-inferior" to operative management for **acute, uncomplicated appendicitis**

Features that should prompt *OPERATIVE* management:

- Appendicolith (+/-)
- Perforation
- Abscess
- Suspicion of tumor
- Peritonitis
- Serious systemic illness

CODA: N Engl J Med. 2020; APPAC: JAMA. 2018; Pediatr Surg Int. 2020

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Risks and Benefits

30-50% of patients initially managed with antibiotics required appendectomy within 5 years

Long term follow up suggests overall equivalent patient satisfaction

For the ID Boards:
know when to recommend surgery

Quality of Life and Patient Satisfaction at 7-Year Follow-up of Antibiotic Therapy vs Appendectomy for Uncomplicated Acute Appendicitis: A Secondary Analysis of a Randomized Clinical Trial. JAMA Surg. 2020

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54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

- Non-operative management of acute appendicitis may be considered if *uncomplicated*
  - Features which should prompt immediate surgery: perforation; abscess; suspected tumor; peritonitis; systemic illness
- Up to 50% will require subsequent appendectomy
- *ID board potential* – recognize when an operation is NEEDED

Appendicitis

Take Home Points

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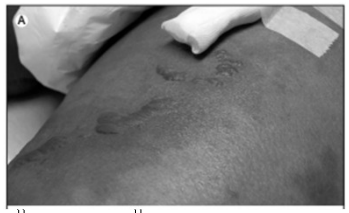
Question #7



Lancet Infect Dis. 2008 Jun;8(6):399.

- A 44-year-old male with a history of cirrhosis due to Hepatitis B and alcoholism presents with fever, lethargy and leg swelling. On exam, he is febrile, hypotensive and tachycardic. Skin exam is as pictured.

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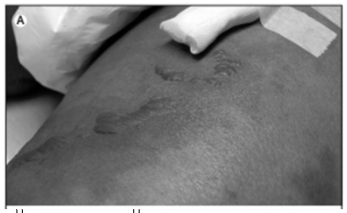
Question #7



Lancet Infect Dis. 2008 Jun;8(6):399.

The patient's clinical syndrome was most likely caused by which of the following exposures?

A. Rat bite
B. Tick bite
C. Consumption of raw oysters
D. Consumption of raw egg

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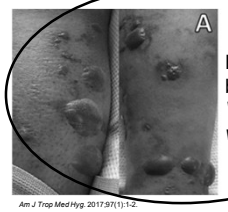
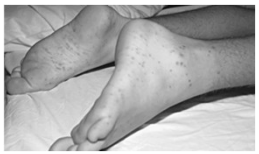
Explanation



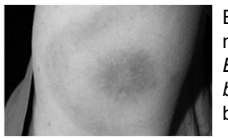
Hemorrhagic bullae from *Vibrio vulnificus*

Am J Trop Med Hyg. 2017;97(1):1-2.



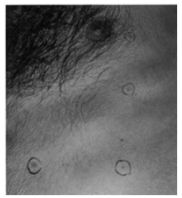
Petechial rash from *Streptobacillus moniliformis* (rat bite fever); fever, rash, migratory arthritis

CMAJ. 2006 Aug 15;175(4):354.



Erythema migrans due to *Borrelia burgdorferi* (tick borne)

https://www.cdc.gov/lyme/signs-symptoms/lyme-disease-rashes.html?CDC_AAref_Val=https://www.cdc.gov/lyme/signs_symptoms/rashes.html



Rose spots from *Salmonella typhi*

Rose spots in typhoid fever. Arch Dermatol. 1972

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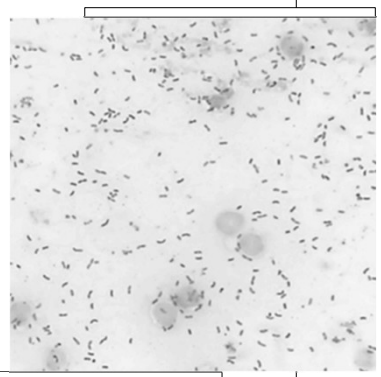
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD



Skin Manifestations of Primary *Vibrio vulnificus* Septicemia. *Am J Trop Med Hyg.* 2017.

Vibrio vulnificus

- Gram-negative, curved bacillus
- Halophilic (salt loving) – *brackish water*
- Cause: *consumption of raw seafood (oysters) or contamination of open wound*
- At risk: *liver disease* (cirrhosis); iron overload; renal disease; immunosuppression
- High mortality

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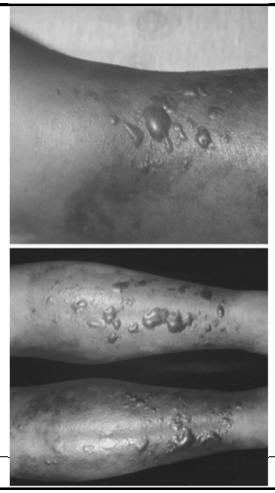
Clinical Presentation and Treatment



Principles and Practice of Infectious Diseases, 9th ed.

- Abrupt onset
- Fever, hypotension
- Rapidly progressive skin lesions: erythema → ***hemorrhagic bullae*** → necrosis
- Bacteremia common
- Treatment:
  - 3rd generation cephalosporin *plus* doxycycline OR fluoroquinolone
  - Debridement (for necrotizing fasciitis)

50

50

- Epidemiology: consumption of raw oysters; contamination of wound (organism lives in warm, brackish water)
- At risk: liver disease, iron overload states (also chronic kidney disease; diabetes or other immune suppression)
- Clinical presentation: rapidly progressive skin lesions with *hemorrhagic bullae; fever, hypotension, sepsis*
- Diagnosis: clinical; blood cultures usually positive
- Treatment: 3rd generation cephalosporin plus doxycycline or fluoroquinolone; debridement

Vibrio Vulnificus

Take Home Points

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Question #8

- A 38-year-old female travels to Bangladesh for a friend's (outdoor) wedding.
- She has never traveled to this region. In preparation for the trip, she received Typhoid vaccine and was started on malaria prophylaxis with doxycycline.
- Five days after returning home, she develops fever, headache and diffuse muscle and joint pain.
- Over the next few days, a rash develops – beginning on the dorsum of her hands and feet with spread to her arms, legs and torso.
- She presents to urgent care for evaluation.

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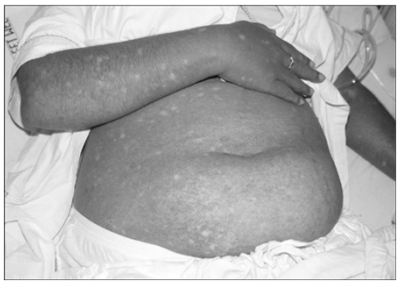
54 Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

Question #8



Indian J Dermatol. 2010;55(1):79-85.

- Physical exam is notable for fever (101.2 degrees Fahrenheit) and a diffuse, morbilliform rash.
- CBC is as follows:
  - WBC 3.26 x 10^9 / L (normal)
  - Hgb 12.9 g/dL (normal)
  - Platelets 113,000 / mcL (low)
- A comprehensive metabolic profile is normal including renal and liver function tests.

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Question #8

Which of the following tests is most likely to yield the diagnosis?

A. *Dengue* real-time PCR
B. Blood culture
C. *Lyme* enzyme immunoassay (EIA)
D. *Malaria* rapid diagnostic test (RDT)

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Dengue is Common Worldwide…and Rising

- 100-400 million infections each year worldwide
- Tropical and subtropical climates
- Urban and semi-urban areas

https://www.cdc.gov/dengue/outbreaks/2024/index.html

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Dengue in Non-travelers

- Local transmission has been observed in US (Florida, Hawaii, Texas, Arizona, California)
- Transmission: human-mosquito-human

https://www.cdc.gov/dengue/outbreaks/2024/index.html

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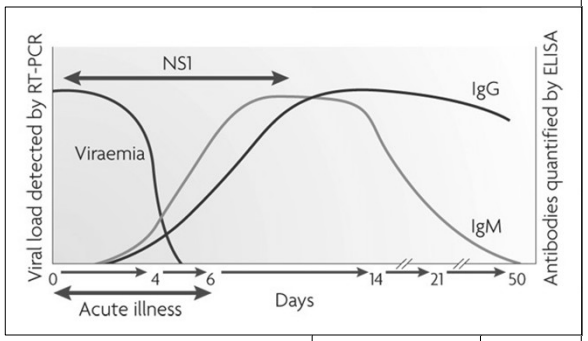
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Dengue: Diagnostic Testing



Preferred: nucleic acid testing (**PCR**) within first 5 days

Other:

- *NS-1 antigen*: less sensitive and only positive early in course
- *Serology*: may cross-react; must confirm early IgM with later IgG

Guzman, M. G. et al. Dengue: A continuing global threat. Nature Reviews Microbiology 8, S7–S16 (2010).
https://www.cdc.gov/dengue/hcp/diagnosis-testing/index.html

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Severe Dengue

- Symptoms typically improve in 1-2 weeks
- May progress to severe Dengue (as rash and fever disappear)
- Risk increased if prior infection (with another serovar)
- Signs of severe dengue:
  - Hypotension / shock
  - Hemorrhage (mucosal / GI bleeding)

https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
https://www.cdc.gov/dengue/hcp/clinical-signs/index.html

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Aedes aegypti mosquito, image from https://www.cdc.gov/mosquitoes/about/life-cycle-of-aedes-mosquitoes.html

Mosquito-borne Illnesses in a Returning Traveler

For the boards, know:

- Typical epidemiology
- Clinical presentation
- Vector
- Diagnostic approach

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Key Features of Mosquito-borne Illnesses

	Epidemiology	Vector	Clinical Features
Chikungunya	Africa, the Americas, Asia, Europe, islands in Indian and Pacific Oceans; prominent outbreak Caribbean 2013	***Aedes** aegypti* (*A. albopticus* in Europe)	Fever and **joint pain**; rash less common. Symptoms may last months.
Dengue	Worldwide in tropics / subtropics 4 serotypes; infection with a 2nd serotype → severe illness	***Aedes** aegypti* (or *A. albopticus*)	Fever, **headache**, **rash**, **muscle and joint pain** Severe: **shock** / **hemorrhage**
Zika	Prominent in Americas ~2017, then more widespread (Caribbean, Africa, India)	***Aedes** aegypti* **Also sexual transmission; maternal-fetal infection**	Often asx; fever; **rash** (starts on face); **conjunctivitis** Fetal anomalies (**microcephaly, blindness**)

CDC; PPID 9th edition

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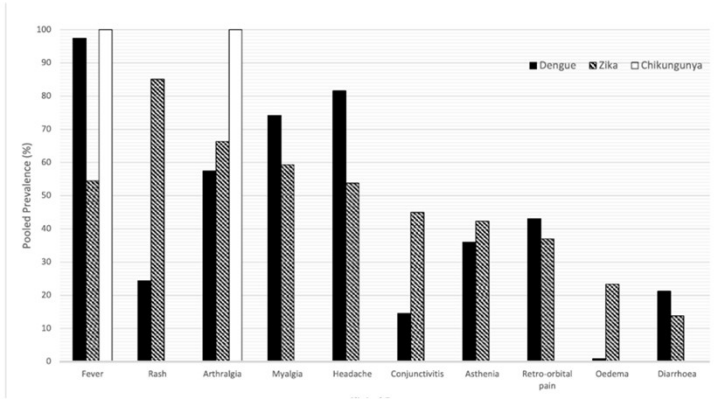
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Comparing Sxs of Dengue, Zika, Chikungunya



Kharwadkar S, Herath N. Clinical manifestations of dengue, Zika and chikungunya in the Pacific Islands: A systematic review and meta-analysis. Rev Med Virol. 2024 Mar. 61

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(Not So) New and Notable: Oroupouche Virus

- *Orthobunyavirus* genus
- Transmitted by *Culicoides paraensis* (midge) and possibly mosquitos
- Typically, in South and Central America → more recently Cuba, Dominican Republic, US (returned travelers)

https://www.cdc.gov/oropouche/stories/meet-the-midge.html

A Comprehensive Review of the Neglected and Emerging Oropouche Virus. Viruses. 2025

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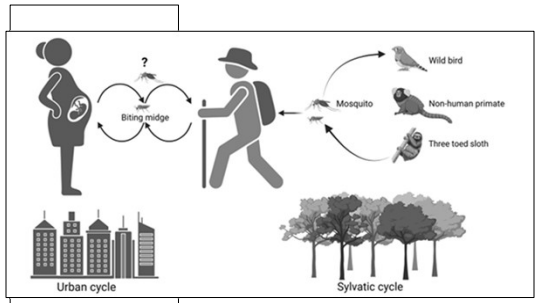
Oropouche Virus

- **Clinical features**: **fever**, headache, myalgia, arthralgia
  - Rash *not* common
  - Rarely, encephalitis
  - **Fetal anomalies** (microcephaly, fetal demise)
- **Diagnosis** – PCR within first 5 days



A Comprehensive Review of the Neglected and Emerging Oropouche Virus. Viruses. 2025 63

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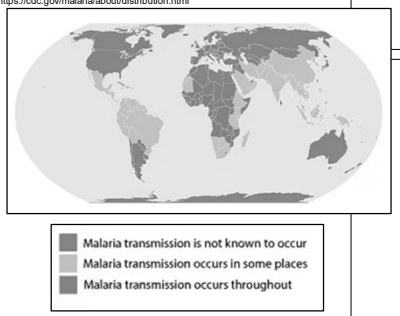
https://cdc.gov/malaria/about/distribution.html



Malaria

- **Epidemiology**: worldwide, tropics and subtropics
- **Vector**: *Anopheles* mosquito
- **Symptoms**: Fever, headache, N/V, diarrhea; severe: anemia, jaundice, splenomegaly, neurologic
- *Species-specific* features

https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html 64

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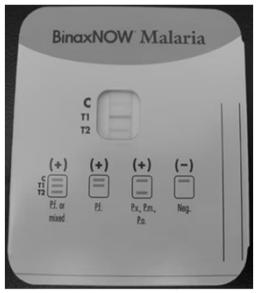

Malaria

- **Epidemiology**: worldwide, tropics and subtropics
- **Vector**: *Anopheles* mosquito
- **Symptoms**: Fever, headache, N/V, diarrhea; severe: anemia, jaundice, splenomegaly, neurologic
- *Species-specific* features
- Microscopy (blood smear); RDT if microscopy not available

https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html 65

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Important Updates on Locally Acquired Malaria Cases Identified in Florida, Texas, and Maryland

HAN HEALTH ALERT NETWORK

HAN This is an official CDC HEALTH UPDATE

Distributed via the CDC Health Alert Network
August 28, 2023, 2:15 PM ET
CDCHAN-00496

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Update to share new information with clinicians, public health authorities, and the public about locally acquired malaria cases identified in the United States. On August 18, 2023, a single case of locally acquired malaria was reported in Maryland in the National Capital Region. This case was caused by the *Plasmodium falciparum (P. falciparum)* species and is unrelated to the cases involving local transmission of *Plasmodium vivax (P. vivax)* malaria in Florida and Texas described in the HAN Health Advisory 494 issued on June 26, 2023. As an update to that report, to date, Florida has identified seven cases and Texas has identified one case of locally acquired *P. vivax* malaria, but there have been no reports of local transmission of malaria in Florida or Texas since mid-July 2023.

https://emergency.cdc.gov/han/2023/han00496.asp#print 66

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Vector borne illnesses have overlapping features; look for keywords

- Dengue, Zika, Chikungunya all spread via *Aedes* mosquitos
  - *Dengue*: headache, rash, "bone-break" pain, low platelets; infxn w/ 2nd serotype → severe dengue
  - *Zika*: may be asx; rash / conjunctivitis common; birth defects
  - *Chikungunya*: prominent joint pain; may become chronic
- Diagnosis:
  - PCR if < 7 d
  - Serology if > 7 d but beware cross-reactivity
- Oropouche: midge; S. America; fever, birth defects; Diagnosis: PCR
- Malaria: *Anopheles* mosquito; fever, anemia, species-specific presentations (*P. falciparum* - severe; *P. vivax / ovale - relapsing)*
  - Diagnosis: blood smear or rapid detection test (RDT)

Vector-borne Illnesses in a Returning Traveler

Take Home Points

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Kitchen Sink Summary

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54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD

Kitchen Sink Summary - 1

Whipple's:

- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- Or PCR of tissue (heart valve for endocarditis)

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html

Acute Rheumatic Fever:

- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

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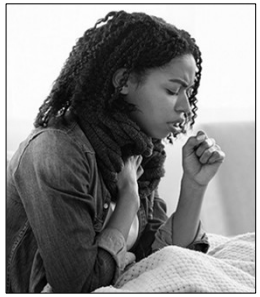
Kitchen Sink Summary - 2

Botulism:

- Due to *C. botulinum* toxin
- Food; infant; wound (black-tar heroin); iatrogenic
- Descending flaccid paralysis (starts with cranial nerves)
- Antitoxin / supportive care



Pertussis:

- Clinical diagnosis: 2+ weeks of cough plus paroxysms, inspiratory whoop, post-tussive emesis, apnea
- Macrolide if within 3 weeks of onset or as PEP for contacts at risk of severe disease

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Kitchen Sink Summary - 3

Appendicitis

- Non operative management may be reasonable for uncomplicated cases
- Identify features that should prompt surgery:
  - Appendicolith +/-
  - perforation
  - Abscess
  - Suspicion of tumor
  - Peritonitis
  - Systemic illness

Asplenia

- Increased risk of infection with encapsulated organisms
- If prompt says asplenia, think…
  - *S. pneumoniae*
  - *N. meningitidis*
  - *H. Influenzae type B*
  - *Capnocytophaga*
  - *Babesia*
  - *Salmonella typhi*
- Prevent infection with immunizations and
- PCN prophylaxis (if < 5 yrs old; recent splenectomy; prior episode of sepsis)

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Kitchen Sink Summary - 4

Vibrio vulnificus:

- Liver disease at risk
- Exposure to raw seafood or contaminated wound (brackish water)
- Rapidly progressive, hemorrhagic bullae / sepsis
- Fluoroquinolone, ceftriaxone, debridement

Vector-borne illnesses in returning traveler

Chikungunya, Dengue, Zika all spread via Aedes mosquitos and can present with fever plus…

- Chikungunya – joint pain
- Dengue – headache, rash, muscle and joint pain; higher risk of severe / hemorrhagic Dengue with 2nd infection
- Zika – rash, conjunctivitis; fetal anomalies; sexual transmission
- PCR if < 7 d; serology cross-reacts

Oropouche: midge; S. America; fever, birth defects; DX: PCR

Malaria: *Anopheles* mosquito; fever, anemia; species-specific presentations; DX: smear or RDT

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54 Kitchen Sink: Syndromes Not Covered Elsewhere

Speaker: Stacey Rose, MD

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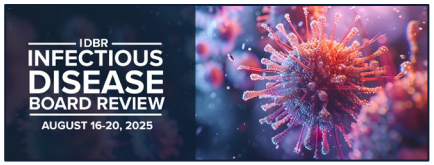
54 Kitchen Sink: Syndromes Not Covered Elsewhere
Speaker: Stacey Rose, MD



Online Materials

Online Only Lectures

#	Duration	Title	Faculty
OL – 1	15 min	How to Prepare for the Certification and Recertification, Including the LKA	Helen Boucher, MD
OL – 2	40 Mins	ID Bootcamp: HIV	Roy Gulick, MD
OL – 3	50 Mins	ID Bootcamp: Transplant	Camille Kotton, MD
OL – 4	45 Mins	Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema	Allan Tunkel, MD
OL – 5	40 Mins	Infections of Upper and Lower Urinary Tract	Barbara Trautner, MD
OL – 6	45 Mins	HIV-Associated Opportunistic Infections III	Rajesh Gandhi, MD
OL – 7	45 Mins	Even More Worms	Edward Mitre, MD
OL – 8	25 Mins	Statistics	Khalil Ghanem, MD
OL – 9	45 min	Epididymitis, Orchitis, and Prostatitis	Barbara Trautner, MD
OL – 10	45 min	Treating Antimicrobial Resistant Infections III Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia	Pranita Tamma, MD
OL – 11	45 min	Antibacterial Drugs Not Covered Elsewhere	Douglas Black, PharmD

Primers and Study Guides

#	Title	Faculty
P – 1	Microbiology Primer	Robin Patel, MD
P – 2	Antibacterial Resistance Primer	Robin Patel, MD
P – 3	Antifungal Resistance Primer	Barbara Alexander, MD John Bennett, MD
P – 4	Antiviral Resistance Primer	Richard Whitley, MD Andrew Pavia, MD
P – 5	HIV Drug Resistance Primer	Roy Gulick, MD
P – 6	Rickettsia Primer	Paul Auwaerter, MD John Bennett, MD
P – 7	Differential Diagnosis of Diseases presenting as Skin Nodules, Ulcers, or Ulceronodular Skin Lesion	David Gilbert, MD
P - 8	Outpatient Antibacterial Drugs	Pranita Tamma, MD

Board Review Question Sets

Title	# Questions
Question Set A	100
Question Set B	100
Question Set C	100
Question Set D	100
Photos Questions	100
Short HIV Therapy Questions	40

Online Only Lectures

OL1

How to Prepare for the Certification and Recertification, Including the LKA

Helen Boucher, MD

TuftsMedicine

How to Prepare for Certification Exams and Longitudinal Knowledge Assessment

Helen W. Boucher MD FACP FIDSA (Hon) FRCPI
Dean and Professor of Medicine
Tufts University School of Medicine
Chief Academic Officer, Tufts Medicine

Tufts | STUART B. LEVY CENTER FOR INTEGRATED MANAGEMENT OF ANTIMICROBIAL RESISTANCE

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Disclosures

- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
  - Sanford Guide

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Website

www.abim.org

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

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

3

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Infectious Diseases Certification

- Initial Certification Exam
- Maintenance of Certification Options:
  - Every 10-year MOC exam
    - Offered 1x/year – Oct 21, 2025, Oct 15, 2026
  - Longitudinal Knowledge Assessment (LKA)
    - Began 2023

https://www.abim.org/maintenance-of-certification/assessment-information/infectious-disease

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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):

  Four 2-hour exam sessions, up to 220 questions, ~ 10 hours
  - Open book: Up to Date allowed

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New(ish) Option: Longitudinal Knowledge Assessment (LKA)

- 5-year recertification period - rolling
- 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 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
- Currently 1,432 ID physicians enrolled

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

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Longitudinal Knowledge Assessment (LKA®) Quarterly Question Schedule (with deadlines)

Enrollment for the LKA **opens 12/1 and closes 6/30.**

QUARTER	OPENS	CLOSES
1	1/1	3/31 at 11:59 p.m. ET
2	4/1	6/30 at 11:59 p.m. ET
3	7/1	9/30 at 11:59 p.m. ET
4	10/1	12/31 at 11:59 p.m. ET

If you are planning to participate in the LKA, it is a good idea to start early so you don't miss any questions. Questions expire at the end of each quarter, and you can't go back to answer them later. Any unopened questions will count against the 100 you can choose not to open over 5 years.

https://www.abim.org/maintenance-of-certification/assessment-information/infectious-disease

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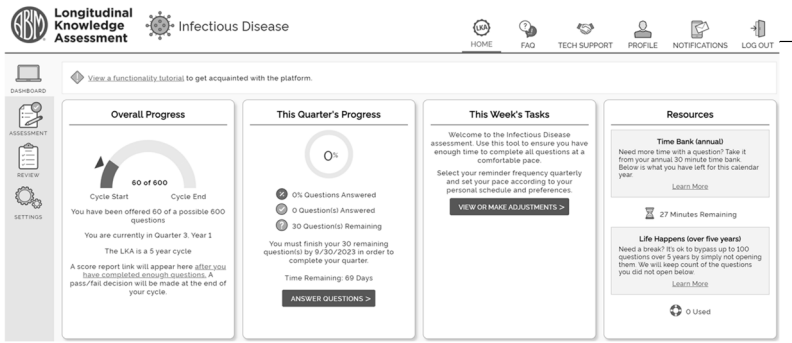

https://www.abim.org/maintenance-of-certification/assessment-information/assessment-options/longitudinal-knowledge-assessment/

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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

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Exam

- Little less than two minutes per question
- Unanswered questions are marked wrong, so guess if you 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

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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 you take a 10-minute break after session one, the amount of break time remaining for the exam is 90 minutes

Note: Proctors monitor entire space (test room, locker rooms, reception)

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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

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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

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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

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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

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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 (note boards 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

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Questions About Exam Day

- Email: https://www.abim.org/contact.aspx
- Call ABIM 1-800-441-ABIM (2246)
  Mon-Fri: 8:30AM – 6PM

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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

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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

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Exam Format

- >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*

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Exam Content

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

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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%

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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

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Clinical Syndromes (cont.)

- 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

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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

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- **Note:**

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

…as an example

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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**

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Exam

- **Takes a 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., H5N1 Bird Flu
- **Things that were hot and now not, are unlikely to appear:**
  - **Anthrax**
- **Effort made not to have "look up" questions:**
  - **e.g., Treatments for uncommon parasitic diseases**
    - **Malaria - yes**
    - **Filariasis – no**

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Pass Rates 1st Time Takers-Initial Certification

Year	# of Examinees	Pass Rate
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%
2021	372	92%
2022	379	94%
2023	407	96%
2024	409	96%

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

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How is MOC 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

30

30

Infectious Diseases MOC Pass Rate

Year	#Examinees	Pass Rate (%)
2015	301	89%
2016	467	94%
2017	350	90%
2018	367	93%
2019	296	91%
2020	216	89%
2021	265	93%
2022	328	95%
2023	263	92%

https://www.abim.org/Media/cqyhgyeo/maintenance-of-certification-pass-rates.pdf

31

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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.)

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What to Do from Now to Exam

- From binders/online 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

33

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Thank You to Jack Bennet and Bennett Lorber

Good Luck To You All !

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Questions, Comments?

- Helen.boucher@tuftsmedicine.org

Tufts CENTER FOR INTEGRATED MANAGEMENT OF ANTIMICROBIAL RESISTANCE

Dr. Helen Boucher

35

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Online Only Lectures

OL2

ID Bootcamp: HIV

Roy Gulick, MD

HIV/AIDS 2025

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

Weill Cornell Medicine
NewYork-Presbyterian

1

Disclosures

- No pharmaceutical or device company relationships
- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel

2

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
- Pathogenesis (<2%)
- Lab testing (<2%)
- HIV Treatment Regimens (4.5%)
- Opportunistic Infections (5%)
- Malignancies (<2%)
- Other complications of HIV (2%)
- Related issues (<2%)

3

Morbidity and Mortality Weekly Report (MMWR): 1981

1981 June 5;30:250–2

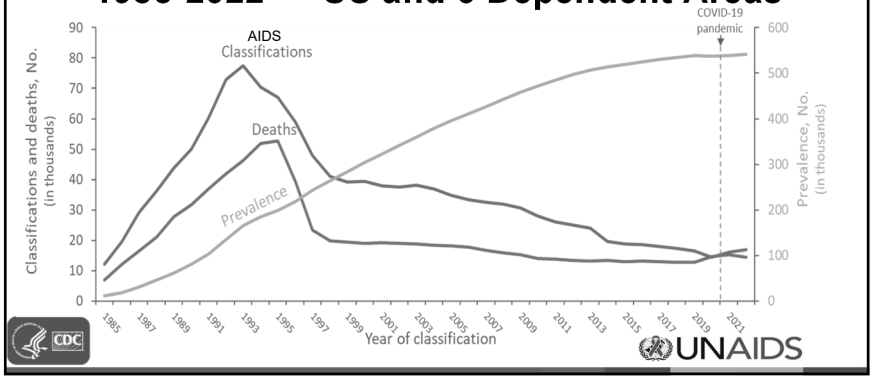
Pneumocystis Pneumonia – Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

2024: >88 million people infected globally; over 1/2 have died

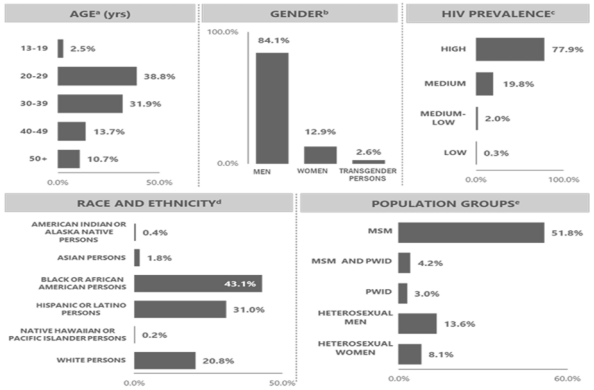
4

AIDS, Deaths, and Diagnosed HIV Infection Ever Classified 1985-2022 — US and 6 Dependent Areas



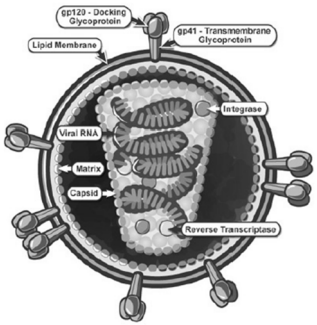
5

HIV Incidence – U.S. (through 9/22)



6

Human Immunodeficiency Virus (HIV)



- Formerly HTLV-III; isolated 1983-4
- Human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- Types: HIV-1 and HIV-2
- Subtypes (clades): B most common in North America and Europe
- Zoonosis from primates (~1900)
- Target cell: CD4+ T-lymphocyte

7

Question #1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

A. ELISA, followed by Western Blot
B. ELISA, followed by HIV RNA
C. ELISA, followed by immunoassay
D. HIV RNA, followed by Western Blot
E. HIV RNA, followed by ELISA
F. HIV RNA, followed by immunoassay

8

Question #1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

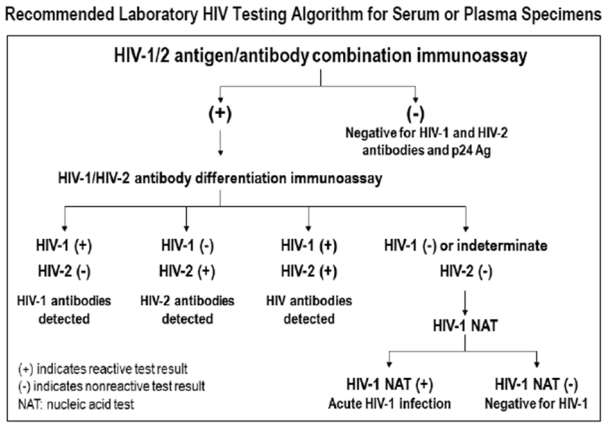
A. ELISA, followed by Western Blot
B. ELISA, followed by HIV RNA
C. **ELISA, followed by immunoassay**
D. HIV RNA, followed by Western Blot
E. HIV RNA, followed by ELISA
F. HIV RNA, followed by immunoassay

9

HIV Testing

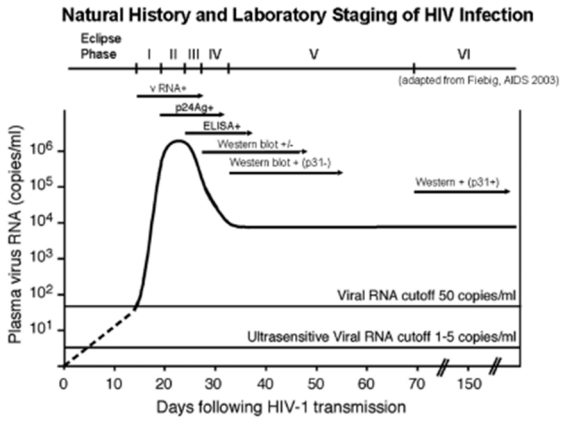
- HIV antibody testing (indirect)
  - Screening test: HIV-1, HIV-2 antibodies by ELISA
  - If repeatedly positive, proceed to confirmatory test
    - Immunoblot (or 2nd HIV rapid test)
  - 20-minute oral test and 1-minute blood test
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)
- Combination antibody + antigen test
  - window period ↓ 3 months → 2 weeks

10



CDC 2014

11



Cohen JID 2010;202:S270

12

Question #2

Who should NOT be routinely offered HIV testing?

A. 32-year-old pregnant woman in a stable relationship
B. 23-year-old sexually active monogamous gay man
C. 75-year-old former injection drug user
D. 10-year-old pre-pubescent girl
E. All of them should be routinely offered HIV testing

13

Question #2

Who should NOT be routinely offered HIV testing?

A. 32-year-old pregnant woman in a stable relationship
B. 23-year-old sexually active monogamous gay man
C. 75-year-old former injection drug user
D. 10-year-old pre-pubescent girl
E. All of them should be routinely offered HIV testing

14

U.S. Preventive Services Task Force (UPSTF) Recommendations

- Screen adolescents and adults ages 15 to 65 for HIV infection
- Screen all pregnant women
- Younger adolescents and older adults who are at increased risk should also be screened
- This is a grade A recommendation ("high certainty that the net benefit is substantial")
- Federal Rule: Private Insurance and Medicare must offer A or B services without a co-pay

Ann Intern Med 2013;159:1-36

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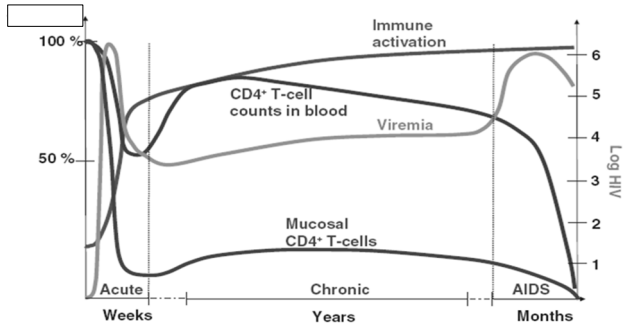
HIV Transmission Risks

Exposure from HIV+ source	Risk per exposure (%)	Risk per exposure (number)
Blood transfusion	93%	9/10
Needle-sharing injection drug use	0.6%	1/167
Percutaneous needle stick	0.2%	1/500
Receptive anal sex	1.4%	1/70
Insertive anal sex	0.1%	1/1000
Receptive penile-vaginal sex	0.08%	1/1250
Insertive penile-vaginal sex	0.04%	1/2500
Oral sex	low	very low
Mother-to-child	23%	1/4

Patel AIDS 2014;28:1509

16

Time Course of HIV Infection



Grossman Nature Medicine 2006;12:289-295

17

CDC Adult AIDS Case Definition

- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added

18

Opportunistic Infections (OI)

- Definition: Infection caused by an organism capable of causing disease only in a host whose resistance is lowered (by other diseases or by drugs)
- AIDS-related:
  - Bacterial: MAC, tuberculosis
  - Fungal: PCP, Cryptococcus, Histoplasma
  - Viral: CMV
  - Parasitic: Toxoplasma
  - Malignancies: Kaposi's sarcoma, Non-Hodgkin's-lymphoma

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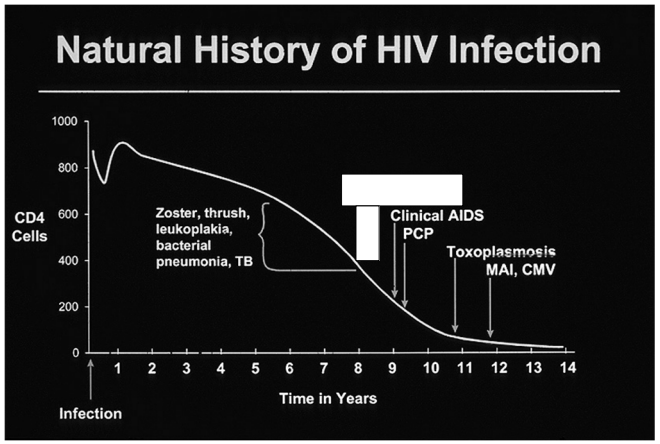
Natural History of HIV Infection



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Goal of Antiretroviral Therapy

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

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When to Start ART?

Guidelines	AIDS/ symptoms	CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
		← asymptomatic →			
US DHHS '24 www.clinicalinfo.hiv.gov	treat	treat	treat	treat	treat
IAS-USA '24 JAMA 2025;333:609-628	treat	treat	treat	treat	treat

U.S. DHHS HIV Treatment Guidelines:

- ART is recommended for all persons with HIV to ↓ morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI)**.
- Initiate ART immediately (or as soon as possible) after HIV diagnosis.

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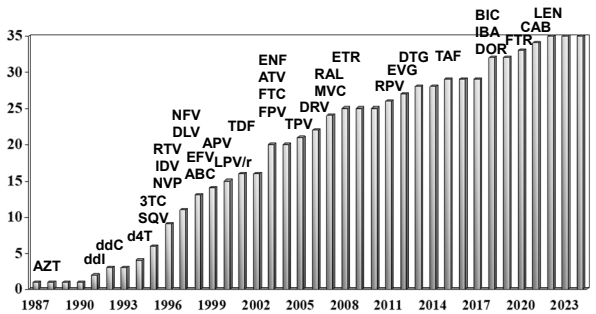
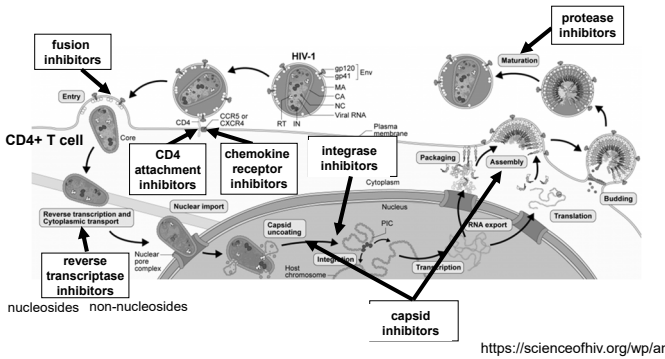
Antiretroviral Drug Approval: 1987-2025



23

Life Cycle of HIV



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

24

Approved ART: 2025*

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

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

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

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

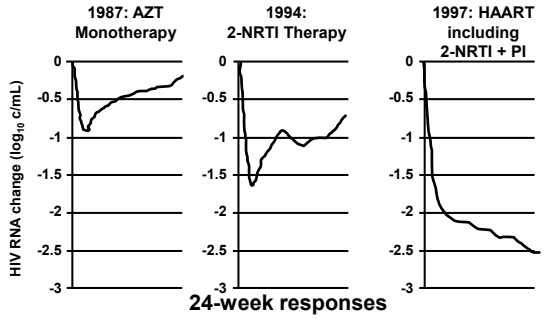
Entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

Capsid inhibitors (CIs)
- lenacapavir (LEN)

*ddI, ddC, d4T, DLV, APV, FPV, and ENF (T-20) discontinued from market

25

Antiretroviral Activity: 1987-1997



Fischl, *NEJM* 1987 Eron, *NEJM* 1995 Hammer, *NEJM* 1996 Gulick, *NEJM* 1997 Cameron, *Lancet* 1998

26

Question #3

Which class of ART is recommended for initial HIV treatment for most patients?

A. All nucleoside analog (NRTI) regimen
B. Non-nucleoside (NNRTI)-based regimen
C. Protease inhibitor (PI)-based regimen
D. Integrase inhibitor (INSTI)-based regimen
E. Entry inhibitor (EI)-based regimen

27

Question #3

Which class of ART is recommended for initial HIV treatment for most patients?

A. All nucleoside analog (NRTI) regimen
B. Non-nucleoside (NNRTI)-based regimen
C. Protease inhibitor (PI)-based regimen
D. Integrase inhibitor (INSTI)-based regimen
E. Entry inhibitor (EI)-based regimen

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What to Start?

Recommended Regimens:

1 or 2 nucleoside analogues + integrase inhibitor
• Bictegravir/tenofovir alafenamide (TAF)/emtricitabine (FTC)
• Dolutegravir + (FTC or lamivudine [3TC]) + (TAF or tenofovir disoproxil fumarate [TDF])
• Dolutegravir/3TC
• With prior cabotegravir (CAB) for PrEP: darunavir/booster (cobicistat or ritonavir) + [(TAF or TDF) + (FTC or 3TC)

Alternative regimens: abacavir-containing, non-nucleoside (NNRTI)-based, protease inhibitor (PI)-based

U.S. DHHS HIV Treatment Guidelines 9/24

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Approved Single-Tablet ART Regimens

TDF/FTC/EFV (2006)

TDF/FTC/RPV (2011)

TDF/FTC/EVG/c (2012)

ABC/3TC/DTG (2014)

TAF/FTC/EVG/c (2015)

TAF/FTC/RPV (2016)

DTG/RPV (2017)*

TAF/FTC/BIC (2018)

TAF/FTC/DRV/c (2018)

TDF/3TC/DOR (2018)

DTG/3TC (2019)

*FDA approved for maintenance therapy

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Cabotegravir (CAB)

- Integrase inhibitor similar to dolutegravir
- Potent in people with HIV (5, 10, 30, 60 mg oral)
  - Spreen HIV Clin Trials 2013;14:192
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112

- U.S. FDA approved the combination of IM CAB + RPV monthly for switch treatment in 2021
  - For patients undetectable on ART without a history of virologic failure, drug resistance, or chronic HBV infection
  - 2022 FDA label amended for every other month dosing and optional lead-in dosing

Overton Lancet 2021;396:1994 + Orkin Lancet HIV 2021;8:e668

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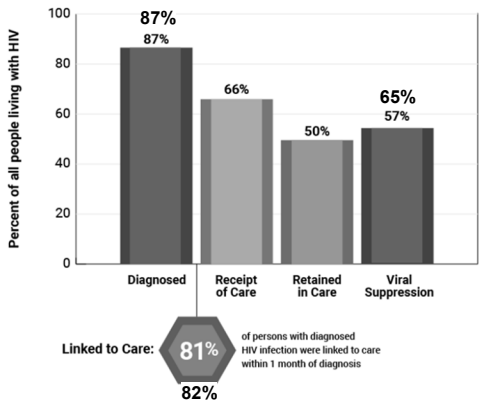
Prevalence-based HIV Care Continuum, U.S. and 6 Dependent Areas, 2019



www.hiv.gov
CDC 2022

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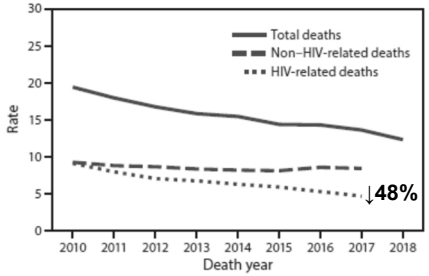
U.S. HIV Deaths: 2010-2018

FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶



Bosh, MMWR 2020;69:1717-24

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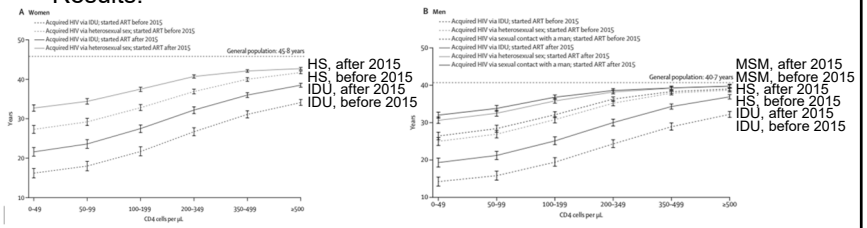
Life Expectancy of HIV on ART

- Goal: To estimate life expectancy of people with HIV on ART for ≥1 year after 2015 at age 40 in North America / Europe
- Study population: ART Cohort Collaboration + UK CHIC Cohort Study (N=206,891 with 5780 deaths)
- Results:



Trickey Lancet HIV 2023;10:e295-e307

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HIV Prevention Strategies

Abstain, **B**e faithful, **C**ondoms,
Counseling & testing

ABC

Immunization ?
Rerks-Ngarm NEJM 2009
others

HSV-2 suppressive treatment ✗
Celum NEJM 2010

Genital tract infection control ✗
☑ Grosskurth Lancet 1995
Wawer Lancet 1999
Kamali Lancet 2003
Gregson PLoS Med 2007

Circumcision ☑
Auvert PLoS Med 2005
Bailey Lancet 2007
Gray Lancet 2007

Diaphragms ✗
Padian Lancet 2007

Exposure prophylaxis with ART ☑
Connor NEJM 1994
Grant NEJM 2010
Baeten NEJM 2012
Thigpen NEJM 2012
Molina NEJM 2015
McCormack Lancet 2016
Landovitz NEJM 2021
Bekker NEJM 2024

Female-controlled microbicides ✗
☑ Abdool Karim Science 2010
Marrazzo NEJM 2015
FACTS 001 CROI 2015

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Question #4

Which PrEP regimen is FDA-approved for at-risk men and women?

A. Daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)
B. Daily tenofovir alafenamide (TAF)/FTC
C. On-demand TDF/FTC
D. On-demand TAF/FTC
E. All of the above

36

Question #4

Which PrEP regimen is FDA-approved for at-risk men and women?

A. Daily tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)
B. Daily tenofovir alafenamide (TAF)/FTC
C. On-demand TDF/FTC
D. On-demand TAF/FTC
E. All of the above

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HIV Prevention Strategy: PrEP

- Pre-exposure prophylaxis
- Strategy of administering HIV medications to uninfected, at-risk individuals
- Optimal drug candidates:
  - potent, safe, tolerable, and convenient
  -  = co-formulated tenofovir/FTC
- 2012: FDA approves TDF/FTC for PrEP
- 2019: FDA approves TAF/FTC for PrEP
- 2021: FDA approves injectable CAB for PrEP
- 2024: Subcutaneous lenacapavir (LEN) studies

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Recent PrEP Studies

Study (reference)	Study population	Design	Results: Reduction in HIV Infection
PROUD McCormack Lancet 2015;387:54-60	544 HIV- MSM in UK	TDF/FTC (daily) immediate vs. delayed	TDF/FTC immediate: **86% reduction**
IPERGAY Molina NEJM 2015;373:2237	400 HIV- MSM in France and Canada	TDF/FTC (on demand) vs. placebo	TDF/FTC: **86% reduction**
HPTN 083 Landovitz NEJM 2022;385:595	4570 HIV- MSM and transgender women globally	TDF/FTC (daily) vs. CAB injections (every other month)	CAB non-inferior and **superior** to TDF/FTC
HPTN 084 Delany-Moretlwe Lancet 2022;399:1779	3224 HIV- at-risk women aged 18-45 in Sub-Saharan Africa	TDF/FTC (daily) vs. CAB injections (every other month)	CAB **superior** to TDF/FTC

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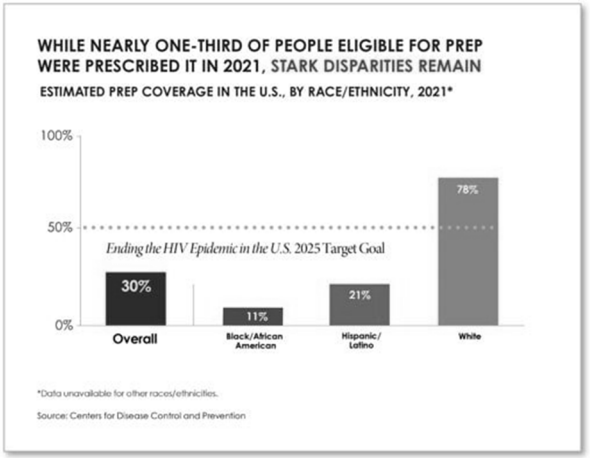

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Federal Plan to End AIDS by 2030

https://www.hiv.gov/ (2019)

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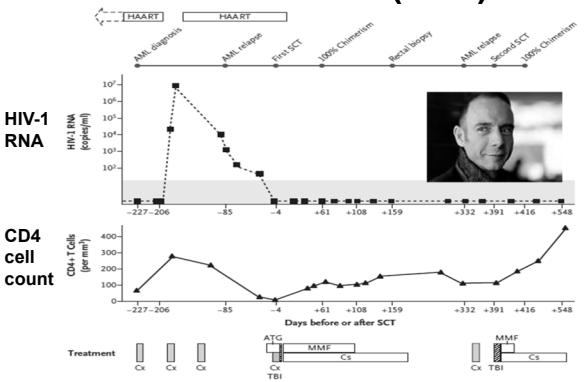
HIV Cure (N=11) 9!



Hutter NEJM 2009;360:692

Cure #2 *first Latino
London
Gupta, Nature 2019;568:244-248
Cure #3 *first woman
NYC
Hsu, Cell 2023;186:1115-1126
Cure #4
Dusseldorf
Jensen, Nat Med 2023;29:583-587
Cure #5
City of Hope
Dickter, NEJM 2024;390:669-671
Cure #6 *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544-3554
Cure #7 *first Δ32 hetero donor
Berlin
Gaebler, et al IAS 2024
Cure #8 *HIV rebound
Chicago
Rubinstein CROI 2025 #531
Cure #9
Oslo
Troseid CROI 2025 #532

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Conclusions

- HIV/AIDS is a worldwide pandemic
- Routine HIV testing should be offered to ALL patients
- Antiretroviral therapy (ART) ↓ HIV RNA, ↑ CD4 cell counts, prevents disease progression, and prolongs healthy survival
- Current ART consists of 2- or 3-drug therapy and is increasingly available worldwide
- Current life expectancy for people with HIV on therapy approaches that of the general population
- Prevention continues to be key
- Cure research is in progress

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Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- NY Presbyterian
- AIDS Clinical Trials Group (ACTG)
- Division of AIDS, NIAID, NIH
- The patient volunteers!

rgulick@med.cornell.edu

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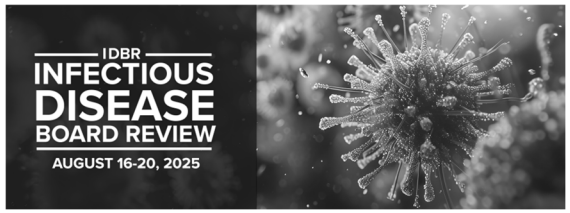
Online Only Lectures

OL3

ID Bootcamp: Transplant

Camille Kotton, MD



Solid Organ and Stem Cell Transplant ID Bootcamp

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
Prior Chair, Infectious Disease Community of Practice, American Society of Transplantation
Prior President, Infectious Disease Section, The Transplantation Society

1

Disclosures of Financial Relationships with Relevant Commercial Interests

Camille Nelson Kotton, Disclosures		
Company	Role	Details
Evrys	Consultant	CMV treatment in transplant
Merck	Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME)	Transplant infections CMV antiviral trial, adjudication Pneumococcal vaccine, adjudication
Shire/Takeda	Consultant, Adjudication committee member, symposium speaker (CME)	CMV management in transplant patients
AiCuris	Research, consultant	Local PI, use of pritelivir in immunocompromised patients with resistant herpes
QIAGEN	Consultant, research, speaker	CMV diagnostics
Roche Diagnostics	Consultant, speaker	Review of risk factors for herpes viral infections after transplant, viral load testing
Kamada	Consultant, research, speaker	Immunoglobulins for CMV, measles
Biotest	Consultant, speaker	Immunoglobulins for CMV

2

Outline: What I Hope You Will Learn

- Type of immunosuppression seen with organ and stem cell transplant
- Timelines of infection
- Prevention is paramount
  - Gaps in prophylaxis help develop the differential diagnosis
- Syndromes
- Diagnostics
  - Differential diagnosis is broad, imperative to obtain diagnosis
- Treatment – including drug interactions
- Latest strategies for prevention, recognition, diagnosis, and treatment
  - Guidelines
  - Best practices for safety and practice improvement
- **Bootcamp: meant as an introduction to subsequent similar talks**

3

Prevalence of Immunosuppression Among US Adults, Martinson & Lapham, JAMA Feb 2024

CDC National Health Interview Survey

6.6% are immunosuppressed
- 4.4% reported immunosuppressive condition
- 3.9% take an immunosuppressive medication
- 1.8% report both immunosuppressive condition and medication

This number has doubled in the past decade

Table. Self-Reported Status of Immunosuppression for 2021

	Unweighted data, No. (%)		Weighted prevalence per 100 US population, % (95% CI)
	Total sample (N = 29 164)	Had immunosuppression (n = 2123)	
Had immunosuppression		2123 (7.2)[a]	6.6 (6.2-6.9)
Sex			
Male	13 246 (45.4)	737 (35.3)	5.2 (4.8-5.7)
Female	15 918 (54.6)	1351 (64.7)	7.9 (7.4-8.4)
Race and ethnicity[b]			
Hispanic	4044 (13.9)	229 (11.0)	5.0 (4.3-5.8)
Non-Hispanic			
African American or Black	3126 (10.7)	222 (10.6)	6.1 (5.2-7.2)
American Indian or Alaska Native	401 (1.4)	43 (2.1)	8.4 (6.0-11.7)
Asian	1774 (6.1)	70 (3.3)	3.7 (2.8-4.8)
White	19 458 (66.7)	1508 (72.2)	7.4 (6.9-7.8)
Other[c]	361 (1.2)	16 (0.8)	4.2 (2.3-7.3)
Age group, y			
18-29	3836 (13.2)	141 (6.8)	3.3 (2.8-4.0)
30-39	4713 (16.2)	224 (10.7)	4.5 (3.8-5.2)
40-49	4341 (14.9)	300 (14.4)	6.6 (5.8-7.4)
50-59	4731 (16.2)	422 (20.2)	8.7 (7.8-9.6)
60-69	5341 (18.3)	514 (24.6)	9.5 (8.6-10.5)
70-79	4059 (13.9)	355 (17.0)	8.9 (7.9-10.0)
≥80	2143 (7.3)	132 (6.3)	6.6 (5.4-8.1)
Health insurance status			
Insured	27 210 (93.3)	2018 (96.6)	6.9 (6.6-7.3)
Uninsured	1954 (6.7)	70 (3.4)	3.0 (2.2-3.9)

4

Defining: **Moderate to Severe Immune Compromise** *honed during the COVID-19 pandemic (USA CDC)*

- **Active treatment for solid tumor and hematologic malignancies**
- **Receipt of solid-organ transplant and taking immunosuppressive therapy**
- **Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)**
- **Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)**
- **Advanced or untreated HIV infection**
- **Active treatment with:**
  - **high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day)**
  - **alkylating agents, antimetabolites**
  - **transplant-related immunosuppressive drugs**
  - **cancer chemotherapeutic agents classified as severely immunosuppressive**
  - **tumor-necrosis (TNF) blockers and other biologic agents that are immunosuppressive or immunomodulatory.**

Factors to consider in assessing the general level of immune competence in a patient include disease severity, duration, clinical stability, complications, comorbidities, and any potentially immune-suppressing treatment.

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

5

Broad Categorization of Examples of Immunocompromised Status Based on Medical Condition or Immunosuppressive Treatment

Risk Category	Example Health Condition	Example Therapeutics
Higher risk immunocompromised patients	• Stem cell transplant <2 y • Graft versus host disease, grade 3 or 4 • Hematological malignancy on therapy • Lung transplant • Fewer than 1% peripheral B-cells assessed in past 6 months	• B-cell depleting agents in past 12 months (eg, rituximab, ofatumumab, ocrelizumab, others) • CAR-T therapy in past 12 months • Abatacept
Moderate risk immunocompromised patients	• Solid organ transplant other than lung • Solid tumor on treatment • Congenital agammaglobulinemia • Graft versus host disease, grade 1 or 2 • HIV infection with CD4 <200 cells/mm^3 • Other severe primary immunodeficiency	• Tyrosine kinase inhibitor (eg, ibrutinib, acalabrutinib, others) • High-dose corticosteroids (>20 mg prednisone or equivalent for >4 wks) • Anthracycline derivates
Lower risk immunocompromised patients	• HIV infection with CD4 >200 cells/mm^3 • Inflammatory bowel disease • Cirrhosis • ESRD • Solid tumor (treatment >12 months prior)	• Anti-TNF • Anti–IL-6 • Anti–IL-12 and -23 • Corticosteroids ≤10 mg long-term, or <20 mg for <4 wks • Intra-articular steroids

2024 Clinical Practice Guideline Update by the Infectious Diseases Society of America on the Management of COVID-19: Anti-SARS-CoV-2 Neutralizing Antibody Pemivibart for Pre-exposure Prophylaxis
Clinical Infectious Diseases, ciae435, https://doi.org/10.1093/cid/ciae435 **Published:** 29 October 2024

6

The Less Immunocompromised Host

- Stem cell transplant recipients > 2 years post-transplant, not on immunosuppressive drugs, no graft versus host disease
- Chemotherapy for leukemia/lymphoma or cancer more than 3 months earlier with malignancy in remission
  - Those who have received immunotherapy with agents such as checkpoint inhibitors may need longer
- HIV patients with >500 CD4 lymphocytes
- Asplenia
- Nutritional deficiencies
- Steroid inhalers, topical steroids, intra-articular, bursal, or tendon injection of steroids, or on high-dose steroids over a month ago

https://wwwnc.cdc.gov/travel/yellowbook/2024/travelers-with-additional-considerations/immunocompromised-travelers. Kotton, Kroger, Freedman

7

"Net state of immunosuppression"

Dr. Robert Rubin,
Massachusetts General Hospital

IMMUNOSUPPRESSION IS ADDITIVE/A COMPOSITE OF RISK FACTORS

- **Disease state** may alter the immune system
  - Autoimmune diseases
  - Advanced organ failure
  - Other organ compromise: kidney, liver
- **Comorbidities/conditions**
  - Diabetes, obesity, malnutrition/weight loss
  - Hypogammaglobulinemia
  - Viral infections (HIV, CMV, EBV, HCV)
  - Altered microbiome
  - Advanced age
- **Exogenous immunosuppression**
  - Pre-transplant immunosuppression (i.e., autoimmune hepatitis)
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection

8

National Organ Transplant Data – USA

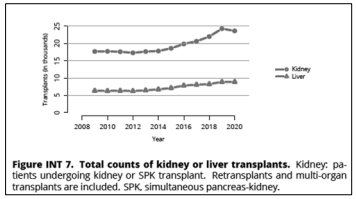


Figure INT 7. Total counts of kidney or liver transplants. Kidney: patients undergoing kidney or SPK transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

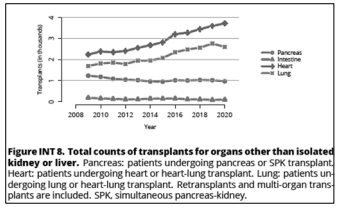


Figure INT 8. Total counts of transplants for organs other than isolated kidney or liver. Pancreas: patients undergoing pancreas or SPK transplant. Heart: patients undergoing heart or heart-lung transplant. Lung: patients undergoing lung or heart-lung transplant. Retransplants and multi-organ transplants are included. SPK, simultaneous pancreas-kidney.

>850,000 transplants done in USA since 1988

OPTN/SRTR 2020 Annual Data Report: Introduction, AJT Feb 2022

9

Types of Stem Cell Transplants: a Spectrum

Autologous stem cell transplant (*lower* infection risk)

- The patient's **own stem cells** are collected before high-dose chemotherapy and then reintroduced after treatment. This allows for high doses of chemotherapy that would otherwise kill the patient's normal blood cells.

Allogeneic stem cell transplant (*higher* infection risk)

- **Stem cells from a donor**, who can be a blood relative or someone who is not related but is a close genetic match
- **Haploidentical:** stem cells from a "half-matched" donor
- **Cord blood:** stem cell found via an umbilical cord blood bank
- **Reduced-intensity** allogeneic stem cell transplantation (also called **mini-transplant** or **nonmyeloablative** transplant): conditioning treatment contains lower, less toxic doses of chemotherapy and radiation

10

Total Number of HCTs Performed in the United States

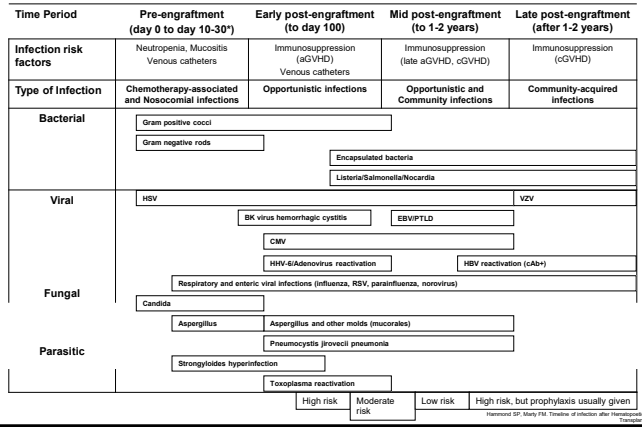
Center for International Blood and Marrow Transplant Research, 2016-2020

Donor Type	Number	%
Autologous:	*66,458*	*59%*
Allogeneic:		
HLA-Matched Sibling	10,792	10%
Other Related Donor	10,037	9%
Unrelated	24,697	22%
Total	**111,984**	**100**

https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary
accessed 18 March 2025

11

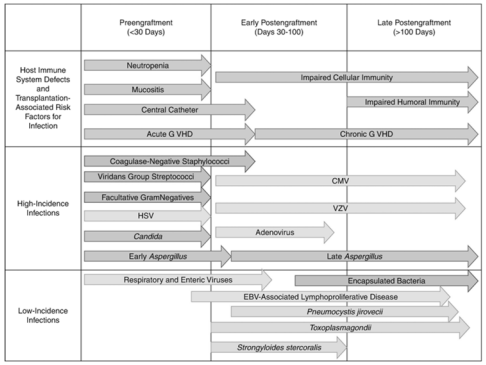
Timeline of Infection after HSCT



Hammond SP, Marty FM. Timeline of infection after Hematopoietic Stem Cell Transplant. In AST Handbook of Transplant Infections, D Kumar A Rubin Eds. 2011.4.

12

Timeline of Host Immune Defects and Infections in Allo-HSCT Recipients



From Pereira MR, Pouch SM & Scully B, *Infections in Allogeneic Stem Cell Transplantation*, Principles and Practice of Transplant Infectious Diseases (2019)

13

Common Immunosuppression after *Allogeneic* Stem Cell Transplant (not Autologous*)

- Chemotherapy
- Anti-graft versus host disease prophylaxis
  - Tacrolimus, cyclosporine
  - Methotrexate
  - Mycophenolate mofetil
  - Antithymocyte globulin (rabbit)
- Anti-graft versus host disease treatment
  - The first-line treatment of acute GVHD is methylprednisolone

* Immunosuppression generally not needed

14

Infectious Complications from CAR-T Cell Therapy

Reference	CAR T-cell therapy	*N*	Underlying malignancy	Severity grade	Timepoint	Bacterial infection incidence (*n*, %)	Viral infection incidence (*n*, %)	Fungal infection incidence (*n*, %)
Abramson *et al.*[28]	Lisocabtagene maraleucel	269	R/R B-cell lymphoma	⩾3	12 months	27/269 (10)	4/269 (1)	2/269 (1)
Locke *et al.*[18]	Axicabtagene ciloleucel	108	Refractory B- cell lymphoma	All	12 months	44/108 (40)	11/108 (10)	7/108 (6)
Logue *et al.*[23]	Axicabtagene ciloleucel	85	R/R B-cell lymphoma	All	⩽30 days	26/85 (31)	12/85 (14)	2/85 (2)
					>30 days	13/85 (15)	19/85 (22)	0/85 (0)
Wittmann Dayagi *et al.*[26]	CD28-based CAR T cells	88	R/R B-cell lymphoma	All	⩽30 days	22/85 (25)	14/85 (16)	0/85 (0)
					30–60 days	8/85 (9)	2/85 (2)	1/85 (1)
Baird *et al.*[27]	Axicabtagene ciloleucel	41	R/R B-cell lymphoma	All	⩽28 days	7/41 (17.1)	8/41 (19.5)	4/41 (9.8)
					>28 days	10/41 (24.4)	10/41 (24.4)	9/41 (22)
Wudhikarn *et al.*[24]	Axicabtagene ciloleucel OR tisagenlecleucel	60	R/R DLBCL	All	⩽30 days	20/60 (33)	10/60 (17)	1/60 (2)
					>30 days	14/60 (24)	17/60 (28)	3/60 (5)
Hill *et al.*[21]	Anti-CD19 CAR autologous T cells	133	ALL, CLL, NHL	All	⩽28 days	22/133 (16.5)	11/133 (8.3)	4/133 (3)
					>28 days	7/119 (5.9)	11/119 (9.2)	2/119 (1.7)
Munshi *et al.*[31]	Idecabtagene vicleucel	54	R/R multiple myeloma	All	12 months	13/54 (24)	15/54 (28)	4/54 (7)

15

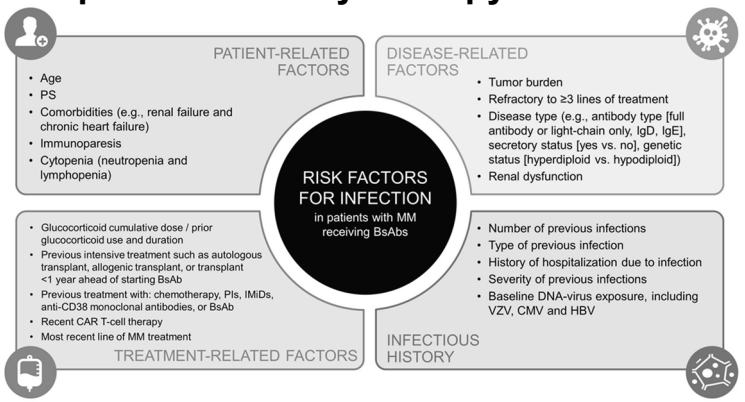
CAR-T Cell Therapy & Infectious Complications

- Chimeric antigen receptor (CAR) T-cell therapy involves lymphocyte engineering to produce CARs directed towards tumor cell antigens
- Can be profoundly immunosuppressed and often cytopenic, via a multitude of patient- and treatment-related factors.
  - ~1/3 patients will suffer a serious bacterial infection in the first 30 days
  - Viral respiratory tract infection (esp late phase) can be severe
    - CMV rare, seen w/in 6 weeks, 5/72 needed treatment*
  - Fungal infection is uncommon (<5%)
- Numerous off-target effects can cause toxicity-related adverse events
  - cytokine release syndrome
  - immune effector cell neurotoxicity syndrome

Stewart AG and Henden AS, Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis. 2021.
*Kampouri E et al, CMV Reactivation and CMV-Specific Cell-Mediated Immunity after Chimeric Antigen Receptor T-Cell Therapy , CID 2023

16

Bispecific Antibody Therapy & Infections



Raje N et al, Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel, Blood Cancer Journal 2023 https://www.nature.com/articles/s41408-023-00879-7

17

National Organ Transplant Data – USA

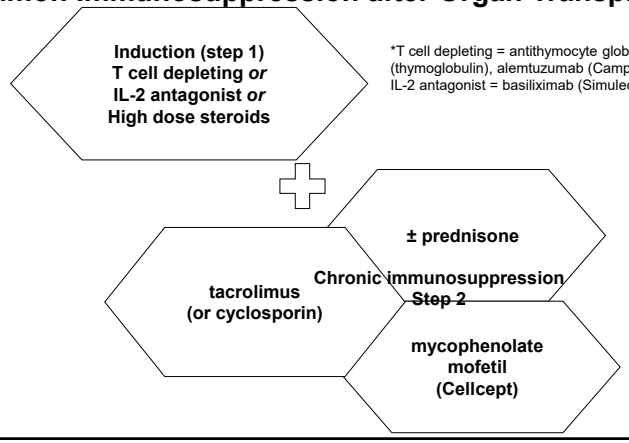
> 1 Million Transplants Done in USA Since 1988

	To Date	2025	2024	2023	2022	2021	2020	2019	2018	2017	2016	2015	2014	2013	2012	2011
All Organs	1,023,665	7,816	48,137	46,629	42,889	41,356	39,036	39,719	36,530	34,770	33,610	30,974	29,540	28,956	28,059	28,553
Kidney	602,288	4,449	27,759	27,332	25,500	24,670	22,817	23,401	21,167	19,849	19,060	17,878	17,108	16,896	16,487	16,816
Liver	224,798	1,941	11,458	10,659	9,528	9,236	8,906	8,896	8,250	8,082	7,841	7,127	6,730	6,455	6,256	6,342
Pancreas	9,514	18	114	102	108	143	135	143	192	213	215	228	245	256	242	287
Kidney / Pancreas	28,748	128	733	812	810	820	827	872	835	789	798	719	709	762	801	795
Heart	97,320	712	4,572	4,545	4,111	3,818	3,658	3,552	3,408	3,244	3,191	2,804	2,655	2,531	2,378	2,322
Lung	55,707	540	3,340	3,026	2,692	2,524	2,539	2,714	2,530	2,449	2,327	2,057	1,925	1,923	1,754	1,822
Heart / Lung	1,588	11	64	54	51	45	58	45	32	29	18	15	24	23	29	27
Intestine	3,577	17	97	95	82	96	91	81	104	109	147	141	139	109	106	129

*UNOS data downloaded 8 April 2025
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/

18

Common Immunosuppression after Organ Transplant



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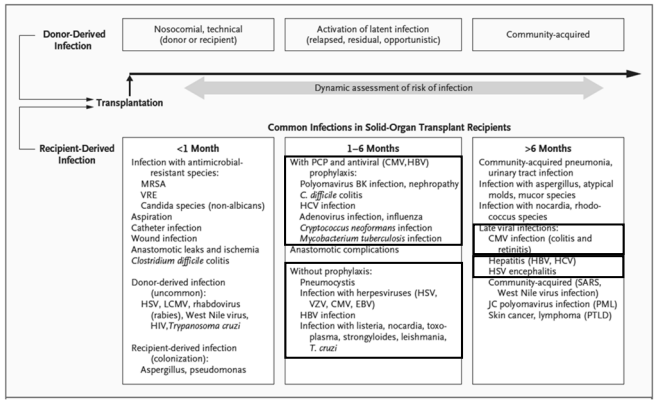
Timeline of Infection after Organ Transplantation



Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

20

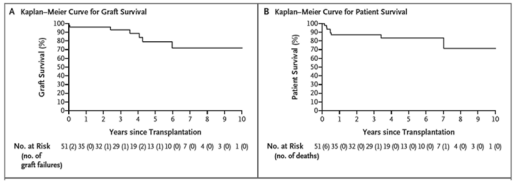
What's Trendy? (Might be on boards?) Hepatitis C Donors and Organ Transplant

- Many programs are using hepatitis C positive donors into negative or positive recipients and treating after transplant
  - Yes, we are infecting people with hepatitis C
- Can be either HCV viral load and/or antibody positive
- For all organs, ~100% clearance
- Was often research protocol, now moving towards standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

21

Longer-Term Outcomes of *HIV-Positive-to-HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug-resistant virus
- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**



22

HIV Organ Policy Equity (HOPE) Act: USA

- **Permits donated, HIV-positive organs to be used for transplantation in HIV-positive patients (only)**
  - Previously prohibited by federal law
- **An active program at multiple centers**
  - Previously research setting only, moving towards standard of care (kidney, liver)
  - Will remain research program for heart and lung transplant (for now)
- **+/- Half of organ donors have false positive HIV testing**
  - Screening test positive, confirmatory test (done later, takes time) negative
- Within 4.5 y, 70% HOPE candidates (n=324) underwent kidney transplant vs 43% non-HOPE*
- 22% of HOPE vs 39% of non-HOPE candidates died or were removed from the waitlist*
- Median transplant wait time: 10.3 months for HOPE vs 60.8 mo for non-HOPE ($P < 0.001$)*
- HOPE candidates had a 3.30-fold higher kidney transplant rate*

*Motter et al, Transplantation 2024

23

Prevention & Prophylaxis: Solid Organ Transplant

- Pre-immunosuppression evaluation**
  - Vaccines
  - Screening for latent infections
  - Plan for chronic infections
  - Optimize diabetes, stop smoking/marijuana use, etc
  - Education
- Management: peritransplant/initiation of immunomodulatory tx
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

24

48yo man referred for routine pre-kidney transplant evaluation, originally from rural El Salvador

Treponemal antibody positive, **RPR 1:16**, never treated, diagnosis = late latent syphilis, treated with weekly benzathine penicillin x 3

***Strongyloides* antibody positive**, 18% eosinophils, diagnosis = indolent strongyloidiasis, treated with ivermectin daily x 2, repeated 2 weeks later

Hepatitis B core antibody positive, surface antibody negative, diagnosis = prior hepatitis B exposure, plan to monitor with HBV DNA (viral load) q 3 months after transplant

TSPOT TB positive (high number spots both ELISpot panels),scattered calcified granulomas on chest CT, diagnosis = latent tuberculosis, treated with isoniazid/vitamin B6 x 9 months

Chagas antibody positive, diagnosis = chronic, late Chagas disease, plan to monitor with Chagas DNA (PCR, parasite load) q month x 3 after transplant then less often

Poorly vaccinated, plan for:
COVID-19 bivalent booster
PCV20 (pneumococcal), Tdap
Quadrivalent influenza vaccine
Shingrix x 2 (shingles)

25

Pre-Immunosuppression Evaluation (MGH)

	Everyone	If risk factors
Hepatitis B surface antigen	x	
Hepatitis B core antibody (IgG not IgM)	x	
Hepatitis B surface antibody	x	
Hepatitis C	x	
HIV	x	
Tuberculosis screening	x	
Coccidioides serology		x
Strongyloides serology		x
Trypanosoma cruzi (Chagas disease)		x

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Pre-Solid Organ Transplant Evaluation (MGH)

	Everyone	Vaccinate if neg	If risk factors
Hepatitis A	x	x	
Hepatitis B surface antigen	x		
Hepatitis B core antibody (IgG not IgM)	x		
Hepatitis B surface antibody	x	x	
Hepatitis C	x		
HIV	x		
Tuberculosis screening	x		
Varicella	x	x	
Cytomegalovirus	x		
Mumps-measles-rubella	x	x	
Syphilis antibody	x		
Coccidioides antibody			x
Strongyloides serology			x
Trypanosoma cruzi (Chagas disease)			x

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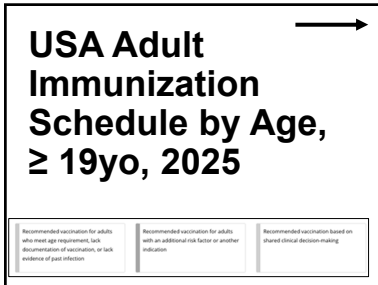
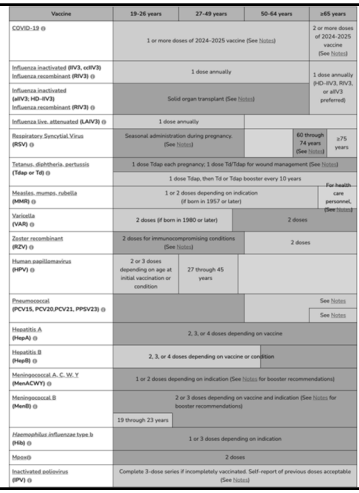
USA Adult Immunization Schedule by Age, ≥ 19yo, 2025

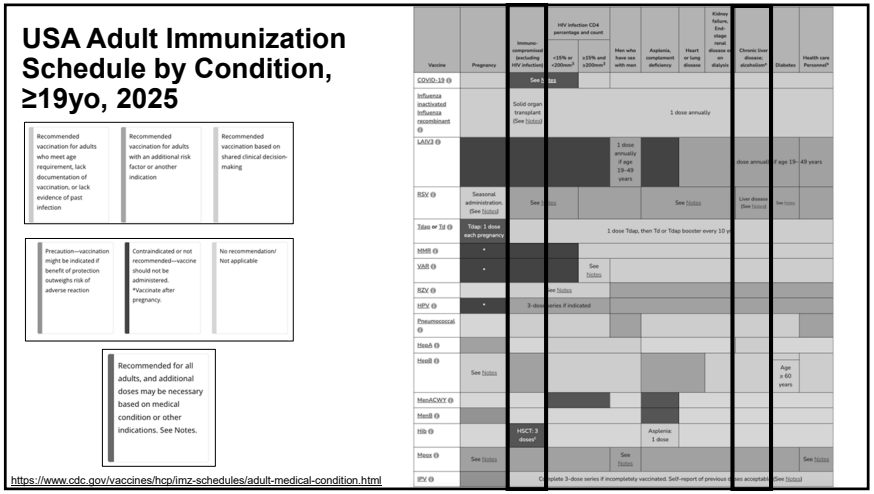




https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html

28

USA Adult Immunization Schedule by Condition, ≥19yo, 2025



https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-medical-condition.html

29

Live vaccines	Severe immunosuppression
Live vaccines	
Bacillus Calmette Guérin (BCG)	Contraindicated
Chikungunya (Ixchiq)	Contraindicated
Cholera (Vaxchora)	No data, generally recommend against use
Ebola (Ervebo)	Consider
Influenza, live attenuated	Contraindicated
Measles-mumps-rubella (MMR/MMR-V)	Contraindicated
Smallpox/mpox (JYNNEOS)	Use as indicated
Smallpox/mpox (ACAM2000)	Contraindicated
Typhoid, Ty21a	Contraindicated
Varicella (adults)	Contraindicated
Yellow Fever	Contraindicated

https://wwwnc.cdc.gov/travel/yellowbook/2024/additional-considerations/immunocompromised-travelers revised for 2026

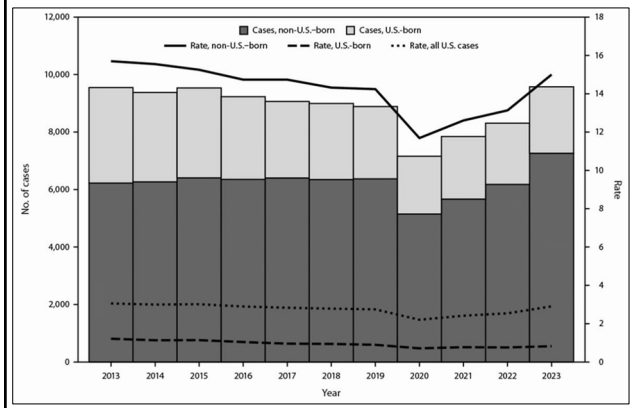
30

CDC: Who Should Get Tested for TB

- TB tests are generally not needed for people with a low risk of infection
- Certain people should be tested for TB bacteria because they are more likely to get TB disease, including:
  - People who have spent time with someone who has TB disease
  - **People with HIV infection or another medical problem that weakens the immune system**
  - People who have symptoms of TB disease (fever, night sweats, cough, and weight loss)
  - People from a country where TB disease is common (most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia)
  - People who live or work somewhere in the US where TB disease is more common (homeless shelters, prison or jails, or some nursing homes)
  - People who use illegal drugs

www.cdc.gov/tb/topic/testing/

31

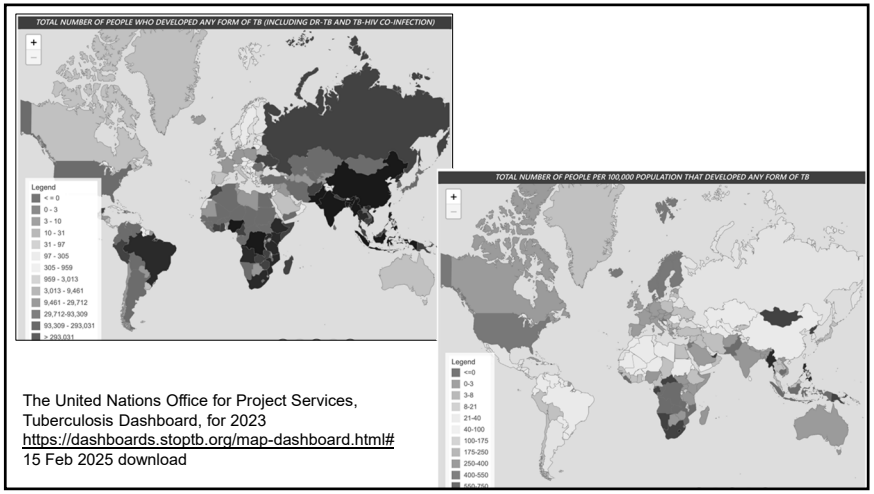


CDC March 2025:

- More than 10,300 tuberculosis (TB) cases were reported in 2024
- An 8% increase from 2023
- Highest case count since 2011

Tuberculosis — United States, 2023, MMWR, March 28, 2024 / 73(12);265–270
https://www.cdc.gov/mmwr/volumes/73/wr/figures/mm7312a4-F_v2-large.gif?_=51657

32



The United Nations Office for Project Services, Tuberculosis Dashboard, for 2023
https://dashboards.stoptb.org/map-dashboard.html#
15 Feb 2025 download

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Latent TB Screening

- Medical history
- Epidemiologic risk factors
- TB skin test (TST)
- Interferon gamma release assay (IGRA) (blood test) (sometimes preferentially vs TST, IDSA guidelines 2016)
  - T-SPOT.®*TB*
  - QuantiFERON®-TB Gold
- Radiographic findings
  - Old granulomatous disease, apical scarring
- *Clinical pearl: search for "granuloma" in the electronic medical record*

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T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

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Question #1

Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.

B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

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B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

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Excellent Prophylaxis is Paramount…

and provides important clues on boards questions

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals

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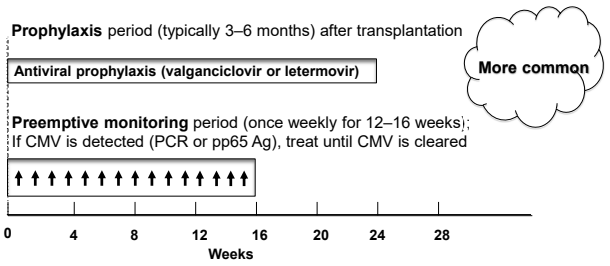
CYTOMEGALOVIRUS PREVENTION: Prophylaxis vs. Preemptive Therapy



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

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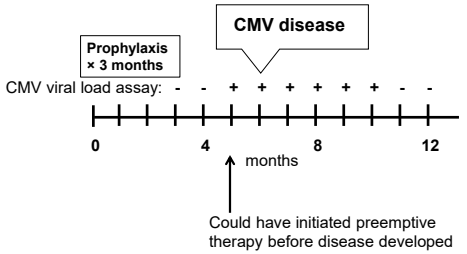
Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based

Consider "net state of immunosuppression"



Kotton CN et al,The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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Prophylaxis: Solid Organ Transplant Massachusetts General Hospital

CMV/Herpes Antiviral Prophylaxis

- Valganciclovir if any CMV risk (if either donor and/or recipient are CMV positive)
  - Prevents CMV, herpes, varicella/zoster
- Acyclovir/valacyclovir/famvir **if no CMV risk**
  - Prevents herpes, varicella/zoster
- Duration varies, 3-6 months is common (longer for lung transplant)
- Main side effect is leukopenia and cost with valganciclovir

Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis	Duration
+	+	Valganciclovir	Antithymocyte globulin and D+R- → 6 months All others 3 months
-	+		
+	-		
-	-	ACV/Famvir/ValACV	

Anti-*Pneumocystis*/anti-bacterial

- Trimethoprim-sulfamethoxazole x 6-12 months (longer for heart/lung transplants)
- *or* dapsone or atovaquone if true allergy

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JAMA | Original Investigation

Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients

A Randomized Clinical Trial

June 2023

Ajit P. Limaye, MD; Klemens Budde, MD; Atul Humar, MD, MSc; Flavio Vincenti, MD; Dirk R. J. Kuypers, MD, PhD; Robert P. Carroll, BM, BCh, DM; Nicole Stauffer, BS; Yoshihiko Murata, MD, PhD; Julie M. Strizki, PhD; Valerie L. Teal, MS; Christopher L. Gilbert, BS; Barbara A. Haber, MD

- D+R- kidney transplants
- Compared letermovir 480mg, orally daily (with acyclovir) or valganciclovir 900mg, orally daily (adjusted for kidney function) for up to 200 days after transplant
- **Confirmed CMV disease: 10.4% on letermovir vs 11.8% on valganciclovir = SAME (17% each, per PI)**
- **Leukopenia (11% vs 37%) or neutropenia (3% vs 17%)** by week 28 lower w/ letermovir vs valganciclovir
- **Quantifiable CMV DNAemia** detected in 2.1% on letermovir vs 8.8% on valganciclovir by week 28
  - Of participants evaluated for suspected CMV disease or CMV DNAemia, none (0/52) who received letermovir and 12.1% (8/66) who received valganciclovir had resistance-associated substitutions.
- Fewer participants in the letermovir group than the valganciclovir group **discontinued prophylaxis** due to adverse events (4.1% vs 13.5%) or drug-related adverse events (2.7% vs 8.8%)
- Valganciclovir dosing adjusted to renal function, details N/A - could explain neutropenia & breakthrough infections
- IMPACT trial comparing 100 versus 200 days of valganciclovir prophylaxis reported **neutropenia** rate of 3% after 100 days and **5% after 200 days (19% leukopenia)**, 15% at some point in trial (Humar et al, 2010)

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MERCK

Media > News releases > News release

June 6, 2023

U.S. FDA Approves New Indication for Merck's PREVYMIS® (letermovir) for Prevention of Cytomegalovirus (CMV) Disease in High-Risk Adult Kidney Transplant Recipients

Important Drug Interactions
Tacrolimus
Cyclosporine
Azoles

US$271 letermovir 480mg/d vs US$117 VGCV 900mg/d per goodrx.com (March 2025)

PREVYMIS® (letermovir) tablets, for oral use
PREVYMIS® (letermovir) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage, CMV Prophylaxis in Kidney Transplant Recipients (1.2)	06/2023
Dosage and Administration, Recommended Dosage for Adult Patients (2.2)	06/2023

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- HSCT: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-transplant. (2.1, 2.2)
- Kidney Transplant: 480 mg administered once daily orally or as an IV infusion over 1 hour through 200 days post-transplant. (2.1, 2.2)

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TABLE 3.
Recommended approaches for CMV prevention in different organs for adult solid organ transplant recipients

Organ	Serostatus	Risk level	Recommended[a]	Alternate
All	D-/R-	Low	Monitoring for clinical symptoms; consider antiviral prophylaxis against other herpes infections	Preemptive therapy (if higher risk, ie, significant transfusions)
Kidney	D+/R-	High	6 mo of (V)GCV or 6 mo of LET or preemptive therapy	High-dose VALACY
	R+	Intermediate	3 mo of VGCV or preemptive therapy	High-dose VALACY. If on mTOR-based immunosuppression, preemptive therapy or close clinical monitoring recommended
Liver	D+/R-	High	3–6 mo of VGCV or preemptive therapy	
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Pancreas	D+/R-	High	3–6 mo of VGCV	Preemptive therapy
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Islet	D+/R-	Intermediate	3 mo of VGCV	Preemptive therapy
	R+	Intermediate	3 mo of VGCV or preemptive therapy	
Heart	D+/R-	High	3–6 mo of (V)GCV	-Preemptive therapy -Some experts add CMVIG to prophylaxis
	R+	Intermediate	3 mo of (V)GCV or preemptive therapy	
Lung	D+/R-	High	12 mo of (V)GCV	-Preemptive therapy
	R+	Intermediate	6–12 mo of (V)GCV	-Some experts add CMVIG to prophylaxis
Intestinal, composite tissue	D+/R-	High	Minimum 6 mo (V)GCV	-Preemptive therapy
	R+	High	3–6 mo (V)GCV	-Some experts add CMVIG to prophylaxis

Kotton CN et al, The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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Lung	D+/R-	High	12 months of GCV/VGCV	-Preemptive therapy
	R+	Intermediate	6-12 months of GCV/VGCV	-Some experts add CMVIG to prophylaxis

4th International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation
Confidential, accepted for publication

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Antiviral Prophylaxis: Stem Cell Transplant

- Acyclovir/valacyclovir/famvir for everyone
  - Prevents herpes, varicella/zoster
  - Duration varies a lot across programs, 6-12+ months is common
- **Letermovir** x 100 days if higher CMV risk
  - if recipient is CMV positive – opposite of solid organ (D-R+ is high risk after HSCT)
  - Prevents CMV, NOT herpes, varicella/zoster
  - Decreased mortality
  - **If small viral load "blips", carry on and retest a week later – only stop therapy if high blips (>1,000 IU/ml)**
  - Main side effect is cost

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Antiviral Prophylaxis/Treatment Agents

Antiviral agent	CMV	HSV	Varicella	BK	Adeno-virus	EBV
Commercially available						
ganciclovir IV/valganciclovir PO	x	x	x			
acyclovir/valacyclovir/famciclovir*	high dose +/-	x	x			
letermovir	**x**					
maribavir	**x**					*in vitro*
foscarnet**	x	x	x			
cidofovir**	x	x	x	poor	+/- (IC50)	
Novel/investigational antiviral agents (SOT)						
brincidofovir (not available)	*x*	*x*	*x*	*x*	*x*	*x*

*acyclovir/valacyclovir/famciclovir and letermovir for prophylaxis only
**foscarnet, cidofovir not usually used for prophylaxis

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When should we use letermovir prophylaxis? My opinion…

Stem cell transplant recipients at high to moderate risk

In SOT recipients who truly cannot tolerate valganciclovir

As secondary prophylaxis after treatment of resistant CMV

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Pneumocystis/Toxoplasmosis Prophylaxis

- First line:
  - Bactrim SS daily or DS three times a week
- Second line (only if real Bactrim allergy or intolerance) alternatives:
  - Atovaquone (Mepron) 1500 mg QD
  - Dapsone 100 mg QD
    - √ G6PD
    - watch for methemoglobinemia, low white blood cell count
  - Pentamidine IV q month (does not cover Toxoplasmosis)
- Duration variable, usually until end of PPx

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Approach to Toxoplasmosis Prophylaxis

- Toxoplasmosis risk highest in Donor +/Recipient seronegative = 50-75% risk of symptomatic infection without prophylaxis within 3 months of heart transplant (much lower with other organs)
- ~7% of Americans age 12-49y are seropositive (https://www.ncbi.nlm.nih.gov/pubmed/25012250)
- Infection more common in patients from endemic regions (e.g., France, Caribbean)
- Can present in any organ system (CNS abscess, pneumonia, myocarditis, disseminated disease)
- Very rare with good prophylaxis

Duration of prophylaxis based on serologic combinations (MGH)			**Prophylaxis**
Serologies	Risk group	Duration of therapy	
D+/R-	Highest risk	Lifetime, if possible (otherwise discuss with infectious disease)	First line: FIRST YEAR: -Bactrim DS 1 tab QD x 1 year (for D+/R-) -Can dose reduce the DS to SS if CrCl<30 -Bactrim SS 1 tab QD (for all other serology; no need to dose reduce this dosage with renal failure/HD) AFTER FIRST YEAR: Bactrim SS 1 tab QD (see columns to left) Second line (only if real Bactrim allergy): Atovaquone (mepron) 1500 mg QD Third line (both Bactrim and mepron allergy): Dapsone 100 mg QD √ G6PD and watch for MetHgb
R+ (regardless of donor status)	Moderate risk	Can stop at one year, or when on low-dose prednisone 5 mg a day, whichever is later/longer.	
D-/R-	Lowest risk		

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Antifungal Prophylaxis: Solid Organ Transplant

Organ	**Common Practice**	**Comments**
Kidney, liver, heart	None for most; some programs give fluconazole/echinocandins peri-liver	Some Nystatin swish and swallow
Pancreas	Fluconazole post-op for variable time, < 1 month	
Lung	**Voriconazole, posaconazole, itraconazole for variable times after transplant**	Voriconazole and augmented skin cancer, osteitis risks a major concern
Intestinal transplant, Composite tissue	Often longer courses of fluconazole/echinocandins	

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Antifungal Prophylaxis: Hematopoietic Stem Cell Transplant

- Fluconazole often used in first 100 days after HSCT
  - Generally, for higher risk receipts
  - Classic population for *C. krusei,* R to fluconazole
- Posaconazole generally reserved for higher risk patients
  - Only FDA approved agent for this indication
- Voriconazole – higher risk of mucormycosis reported
- Isavuconazole – not approved for prophylaxis, but often used, less drug interactions and no QT interval prolongation

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Pearls on Antifungal Therapy

- Voriconazole: when used longer term
  - Higher risk of skin cancers
  - Osteitis
  - Pseudoporphyria in sunlight
  - Best pick for Scedosporium sp (as part of initial therapy)
  - Does not cover mucormycosis
  - Levels variable
- Isavuconazole
  - Reduce drug interactions
  - Reduced QT prolongation
- Posaconazole
  - Usually covers mucormycosis (lower MICs than isavuconazole)

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Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

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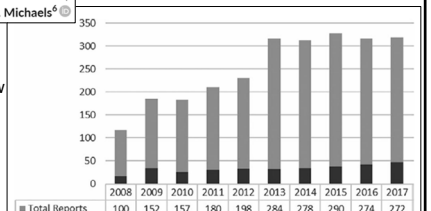
Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[2] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[6]

- The Organ Procurement and Transplantation Network (OPTN) created The Disease Transmission Advisory Committee (DTAC) to review and classify reports of potential disease transmission to inform national policy and improve patient safety.
- January 1, 2008 to December 31, 2017, DTAC received 2185 reports
  - 335 (15%) classified as a proven/ probable donor transmission event
- ~2/3 infection, ~1/3 malignancy
- **Overall risk 17.8/10,000 or 0.178%**
- **All types of infections (!)**
- **Note: initial trigger is transplant center reporting to local organ bank (you!)**



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total Reports	100	152	157	180	198	284	278	290	274	272
Proven/Probable	17	34	26	31	33	32	35	38	42	47

FIGURE 2 Total reports of potential donor transmission events by year

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Examples of Severe Transfusion-transmitted Infections in Solid Organ Transplant Recipients

Infectious agent	Organ transplant	Total blood units given	Infected blood component	Timing of transfusion	Incubation	Recipient outcomes	Reference	Year
WNV	Heart	174	Apheresis platelets	Perioperative period	2 weeks	Severe neurological impairment	Murtagh et al [33]	2002
Yellow fever vaccine virus	Kidney (2) Heart Liver	N/A	Blood transfusion (received by donor)	27 days prior to organ donation (received by donor)	4 weeks 17 days 15 days	Dead (1) Dead Recovered	Gould et al [36]	2021
HIV	Kidney	Unspecified	Fresh frozen plasma	Unspecified	Recipient asymptomatic	Commenced on antiretroviral therapy	CDC [58]	2008
Trypanosoma cruzi	Kidney	1	Apheresis platelets	4 months prior to transplantation	>2 years	Dead	Ries et al [70]	2008

From Stewart AG & Kotton CN, Impact of Blood Donation Biovigilance and Transfusion Transmitted Infections on Organ Transplantation, accepted for publication, Transplant ID, 2024

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TABLE 1 Proven and probable infection transmissions by type (by number of pathogens/syndromes in proven/probable donors) 2008-2017

Category of Infection	Pathogen		Total p/p: (percent of p/p by category)	Comment
Viral	Cytomegalovirus	Fungal (2)	*Aspergillus*	7 (13)	
	Hepatitis B virus		Mucorales	2 (4)	(one cotransmission with *Aspergillus*)
	Hepatitis C virus		*Candida*	13 (24)	
	Lymphocytic chorio		Coccidioidomycosis	10 (19)	
	Community respira		Histoplasmosis	7 (13)	
	Parvovirus		*Cryptococcus*	11 (20)	
	West Nile virus		Other	4 (7)	*Scopulariopsis* (1), *Trichosporon* (1), *Geotrichum* (1), *Microsporidia* (2)
	Other		**Total Fungal**	54 pathogens (22) from 53 donors	
	Total Viral	Mycobacterial	Tuberculosis	9 (4)	
Bacterial (1)	*Gram-positive*	Parasitic	*Strongyloides*	13 (42)	
	Staphylococcus aure		Toxoplasmosis	11 (35)	
	Enterococcus		Trypanosomiasis	3 (10)	
	Other		*Balamuthia*	2 (6)	
	Gram-negative		Other	2 (6)	Amoebic encephalitis (1), Schistosomiasis (1)
	Enterobacteriaceae		**Total Parasite**	31 (12)	
	Pseudomonas		Total Infectious Agents/Syndromes	250 pathogens from 244 donors	
	Other				
	Mycoplasma spp.				
	Other				
	Total Bacterial				

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TABLE 7 Time to presentation of donor-derived infection

	Median (Range)	0-30 days	31-90 days	91-180 days	> 180 days
Viral	48 days (11-776)	LCM WNV (4) RSV	CMV (3) Parvovirus WNV	Hepatitis C	Hepatitis B
Bacterial	14 days (2-45)	Assorted (23)	*Klebsiella*		
Fungal	18 days (5-256)	*Candida* (3) *Coccidioides* (6) *Aspergillus* *Cryptococcus* (4) *Scopulariopsis* Zygomycetes (2)	*Aspergillus* *Coccidioides* (3) Histoplasmosis		*Aspergillus*
Mycobacterial	67 days (8-148)	M. tuberculosis (2)	M. tuberculosis (2)	M. tuberculosis (2)	
Parasitic	50 days (70-145)	*Toxoplasma* *Balamuthia* (5)	*Strongyloides* *Toxoplasma* *Encephalitozoon* (2)	*Strongyloides* (2) *Toxoplasma* *Encephalitozoon* *Balamuthia*	

Abbreviations: CMV, cytomegalovirus; LCMV, lymphocytic choriomeningitis; RSV, respiratory syncytial virus; WNV, West Nile virus.

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Ten years of donor-derived disease: A report of the disease transmission advisory committee

Am J Transplant. 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Michael G. Ison[5] | Susan M. Tlusty[2]

TABLE 8 Summary of key lessons learned

Recognition of donor-derived disease	**Trends requiring future confirmation**
Two thirds of DDI develop symptoms within 30 days of transplantation	Breast cancer and thyroid cancer were not transmitted using current screening protocols
Endemic fungal, parasitic, mycobacterial may be manifest after 30 days	Respiratory viruses, mycoplasma, tuberculosis, aspergillus primarily transmitted to lung recipients
Consider donor exposures in cases of unexpected recipient illness	Bacterial and candida DDI rarely noted later than 30 days posttransplant
Although infections predominate, one third of DDD is noninfectious	D + R- toxoplasma non-heart recipients are at high enough risk to merit prophylaxis
DDD from living donors may occur but is less common than from deceased donors	Peanut allergy rarely transmitted to kidney recipients
	No proven/probable transmissions of atypical mycobacteria or prion disease
	DDD from malignancy (other than renal cell carcinoma) has highest mortality
	MDRO organisms are a common cause of bacterial DDI
Donor evaluation	**System improvements**
Critical evaluation to determine accuracy of listed cause of death	Improve early warning systems and global harmonization to recognize and address emerging trends
Consideration of universal or targeted donor testing (even if results learned posttransplant as early interventions effectively prevent development of disease)	Lengthen and improve follow-up to better attribute death, graft loss
Strongyloides	Active tracking of recipients of donors with findings that suggest risk
Coccidioides	Rapid ability to scale up testing as new pathogens emerge
Cryptococcus	
Improved mechanism for development and evaluation of donor tests	
Reporting	
Critical as profound impact on other recipients because involvement of multiple recipients common allowing for interventions; graft or death loss occurred in about one third of recipients with DDD	
Culture of safety: reporting does not result in penalties unless significant policy violations	
DTAC information benefits all in transplant community	
Morbidity and mortality of DDI significant and attention to OPO or UNOS DDI communications necessary	

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Syndromes

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CMV: the most common pathogen after transplant, one of the "*great masqueraders*"

- Asymptomatic viremia**
- CMV syndrome
- End organ disease:
  - Colitis
  - Pneumonitis
  - Retinitis
- Best diagnosed by CMV viral load
- Best treated with valganciclovir or ganciclovir IV
- Treat to resolution of infection and/or viral load – check weekly
- If low absolute lymphocyte count at end, consider secondary prophylaxis or monitoring

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Pathogens Contribute to Infection Risk: Indirect Effects of CMV

General indirect effects– elevated risks

- Bacterial, fungal, viral infections
- Post-transplant lymphoma (PTLD)
- Cardiovascular events
- New-onset diabetes mellitus after transplantation
- Immunosenescence
- Acute rejection
- Mortality

Transplant-specific indirect effects

- Chronic allograft nephropathy and/or allograft loss after renal transplant
- Accelerated hepatitis C recurrence after liver transplant
- Hepatic artery thrombosis after liver transplant
- Allograft vasculopathy after cardiac transplant
- Bronchiolitis obliterans after lung transplant

Kotton, CMV: Prevention, Diagnosis and Therapy, AJT 2013

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Management of Mild to Moderate CMV Infection-I

Who to treat

If Donor positive/recipient seronegative (highest risk group), likely need to treat if CMV viral load > 500 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If recipient seropositive, likely need to treat if CMV viral load > 1500 - 2000 IU/ml (start at lower level if very low lymphocyte count or potent immunosuppression)

If not starting treatment, recheck all a week later – follow closely to see if better or worse

Diagnostically

Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (not whole blood); **trend until there are two negative/very low (<300 IU/ml) results**, then stop therapy; consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease (especially in high-risk D+R- patients, or with higher immunosuppression).

Best to check CMV DNAemia with same specimen type, on same testing platform and at same lab, as whole blood can be +/- 10x higher (extremely variable) result c/w plasma and test results can vary significantly across different labs and testing platforms; best to pick one lab and use that for comparison.

If CMV DNA level does not fall after 2-3 weeks, consider sending CMV resistance testing. This does not need to be sent after 1 week of treatment where we commonly see some increase in the CMV viral load.

Consider checking total IgG level at the time of initiation of treatment. We would replete if the total IgG level was less than 400 with either CMV immunoglobulin or IVIG.

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Management of Mild to Moderate CMV Infection-II

Therapeutically

Start **valganciclovir** 900mg po q12 hours, renally adjusted as needed

Note: would use intravenous therapy if severe, ophthalmologic, refractory/resistant, or life-threatening disease. Consider using intravenous therapy with significant colitis with concern for malabsorption, or if viral load >100,000 IU/ml.

Consider lowering immunosuppression

If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG (especially if severe or resistant disease)

References

Kotton CN, Kumar D, Caliendo AM, Huprikar S, Chou S, Danziger-Isakov L, Humar A; The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation Society International CMV Consensus Group*.Transplantation. 2018 Mar 29.

Are We There Yet? Impact of the First International Standard for Cytomegalovirus DNA on the Harmonization of Results Reported on Plasma Samples. Preiksaitis JK et al, Clin Infect Dis. 2016 Sep 1;63(5):583-9. doi: 10.1093/cid/ciw370.

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Treatment of CMV: Massachusetts General Hospital

Determine severity of infection

Mild to moderate CMV infection

Valganciclovir (oral) 900mg po q12 hours, renally adjusted

Severe (clinically), ophthalmologic, colitis with severe malabsorption, refractory/resistant, or life-threatening

Intravenous ganciclovir 5mg/kg q12, renally adjusted
Convert to oral treatment when clinically improving

Consider lowering immunosuppression
If total IgG < 400, consider giving either CMV Ig 150mg/kg or IVIG

Check weekly CMV DNAemia (i.e., CMV viral load) on plasma (vs whole blood).
Trend weekly until there are one-two negative/very low (<200 IU/ml) results, then stop therapy.

If CMV DNA level does not fall after 2-3 weeks, consider sending CMV resistance testing.
(This does not need to be sent after 1 week of treatment where we commonly see a small increase in the CMV viral load.)

Consider weekly monitoring after the end of treatment for 8-12 weeks so as to capture early recurrent disease vs restarting prophylaxis (especially in high-risk D+R- patients, or with higher immunosuppression).

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What to do with Very Low Viral Load Cases? (<500-1000 IU/ml Plasma or Whole Blood)

- Treatment not always indicated
- With very low viral loads, I think about:
  - Risk factors for severe viral infection (D+R- versus R+)
  - Net state of immunosuppression
  - Absolute lymphocyte count
  - Likelihood of major disease flare with waiting
  - Ability to reliably repeat testing
- Important to understand issues with diagnostics at very low results
- **Retesting in a week** is key so you know which trend of infection
- Approaches vary widely among clinicians; need to formalize guidance

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Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial

Robin K. Avery, Sophie Alain, Barbara D. Alexander, Emily A. Blumberg, Roy F. Chemaly, Catherine Cordonnier, Rafael F. Duarte, Diana F. Florescu, Nassim Kamar, Deepali Kumar, Johan Maertens, Francisco M. Marty, Genovefa A. Papanicolaou, Fernanda P. Silveira, Oliver Witzke, Jingyang Wu, Aimee K. Sundberg, and Martha Fournier, for the SOLSTICE Trial Investigators

INTRODUCTION

This was a phase 3, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of maribavir compared with IAT in HCT and SOT recipients with CMV infections refractory to most recent treatment, with or without resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir.

STUDY DESIGN

STUDY ENDPOINTS

The primary endpoint was confirmed CMV viremia clearance at the end of Week 8 (regardless of premature treatment discontinuation).

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of Week 8, maintained through Week 16 after receiving exclusively study-assigned treatment.

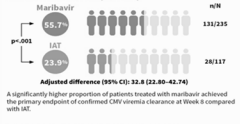
RESULTS

352 patients were randomized (maribavir, n=235; IAT, n=117)

40.1% HCT

59.9% SOT

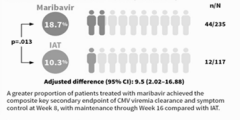
PRIMARY ENDPOINT (WEEK 8)



Adjusted difference (95% CI): 32.8 (22.80–42.74)

A significantly higher proportion of patients treated with maribavir achieved the primary endpoint of confirmed CMV viremia clearance at Week 8 compared with IAT.

KEY SECONDARY ENDPOINT (WEEK 16)



Adjusted difference (95% CI): 9.5 (2.02–16.88)

A greater proportion of patients treated with maribavir achieved the composite key secondary endpoint of CMV viremia clearance and symptom control at Week 8, with maintenance through Week 16 compared with IAT.

SAFETY

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT.

Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% vs 31.9%).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%).

Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%).

One patient per treatment group had fatal treatment-related TEAEs.

CONCLUSIONS

Maribavir was superior to IAT for cytomegalovirus viremia clearance, and viremia clearance plus symptom control, with maintenance of these effects post-therapy in transplant recipients with refractory cytomegalovirus infections with or without resistance.

Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

Clin Infect Dis 2022, ciab988, https://doi.org/10.1093/cid/ciab988

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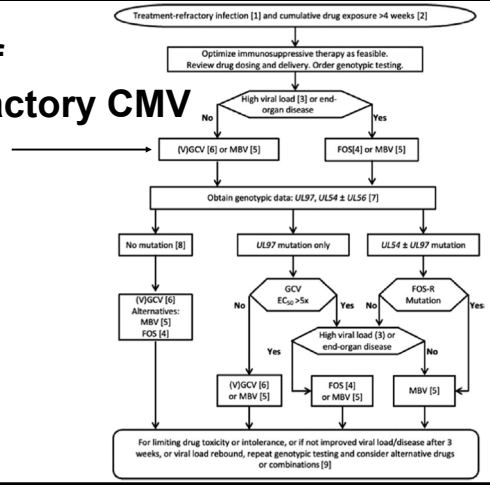
Management of Resistant/Refractory CMV



Kotton CN et al, The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

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The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

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Who Gets Fungal Infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp. liver transplant*surgery
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

1 Shoham S, Marr K. Invasive fungal infections in solid organ transplant recipients. Future Microbio 2012; 7(5): 639-655
2 Singh N, Husain S, Aspergillosis in Solid Organ Transplantation, AJT, 2013

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Diagnostics

- Culture
  - Fungal stain and culture
  - Notify lab not to mince specimen if suspicion of mucormycosis
  - Fungal isolators (blood) very rarely +
    - *Candida* will grow in routine cultures
    - *Histoplasma* better; lysis centrifugation isolators is best
- Pathology: Morphology
  - Septate (*Aspergillus*) vs non-septate (*Mucor/Zygomycetes*) hyphae
  - Grocott-Gomori's (or Gömöri) methenamine silver stain
  - Periodic acid-Schiff (PAS)

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Diagnostics: Fungal Markers

Diagnostic Assay	Specimen	Comments
Cryptococcal antigen	Blood, CSF	High sensitivity/specificity
1,3 beta – D - glucan	Blood	Primarily for yeast; Low sensitivity/moderate specificity *Excellent for Pneumocystis*
Galactomannan	Blood, BAL, other body fluids	Primarily for Aspergillus; Low sensitivity/high specificity on blood, higher sensitivity on body fluids
Aspergillus PCR	Blood, BAL, other body fluids	
Karius Spectrum, a cell-free DNA (cfDNA) test to identify and quantify fungal pathogens	*Blood*	*Uses shotgun metagenomic sequencing* *Higher sensitivity with proven vs probable disease (60% vs 37% Sim BZ et al CID 2025)*

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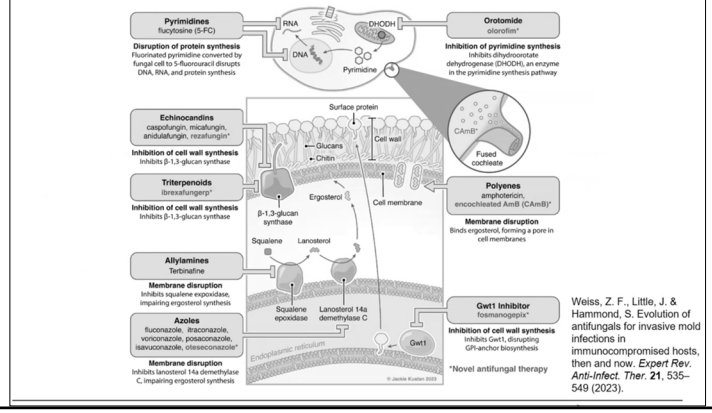
Antifungal Mechanisms of Action



Weiss, Z. F., Little, J. & Hammond, S. Evolution of antifungals for invasive mold infections in immunocompromised hosts, then and now. *Expert Rev. Anti-Infect. Ther.* **21**, 535–549 (2023).

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Clinical Vignette

- 54-year-old woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18

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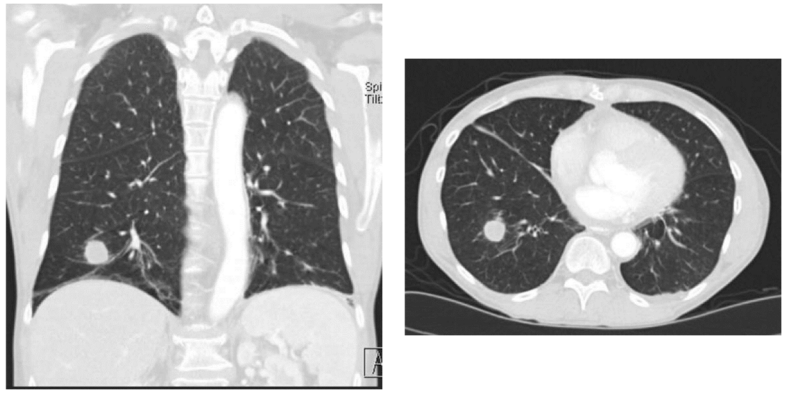

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Question #2

After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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Question #2

After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

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- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well and was quite determined to be discharged in the next few days."
- Voriconazole started
- She underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → **nonseptate hyphae seen**
- **Diagnosis: likely Zygomycetes**
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.

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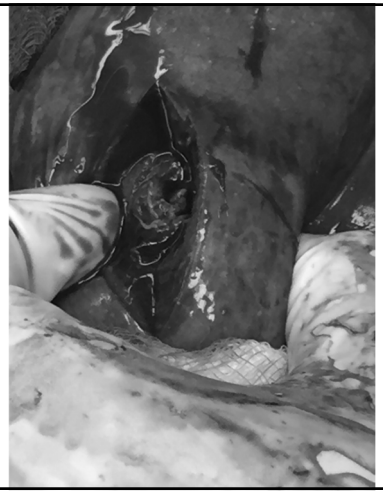

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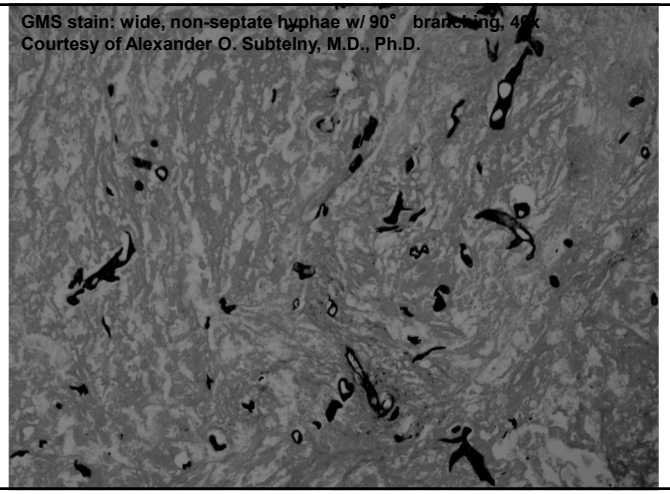

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Very Rare RHIZOPUS SPECIES

SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

MIC DILUTION METHOD

No CLSI interpretive guidelines available

Amphotericin B MIC=1

Isavuconazole MIC=1

Miconazole MIC=2

Posaconazole MIC=0.5

In view of this, Ambisome was stopped on POD #9 and isavuconazole converted to 372mg daily for months/indefinite, plan is for radiographic resolution, immune reconstitution (heart transplant immunosuppression is for life).

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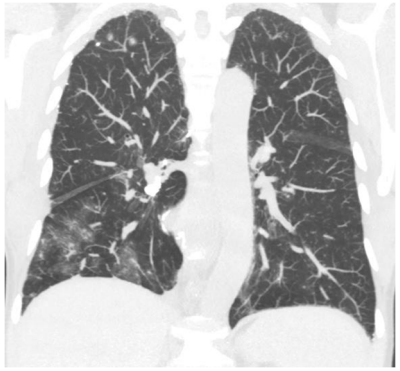

A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.

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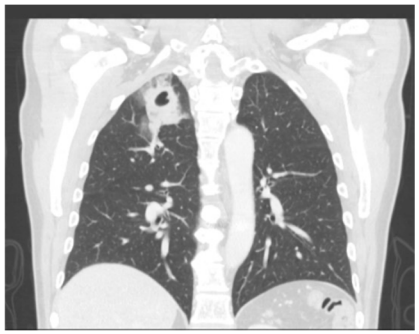
What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all.



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Epidemiology (ID Fellow Note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB - no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs - Denies

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Question #3

What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start “vancopime” (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

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Question #3

What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start “vancopime” (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

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Pseudomonas!

All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

04/19/2021 1657	04/29/2021 1323	Wound culture/smear [818905205] (Abnormal) Other from Biopsy RUL LUNG TBBX

Susceptibility

	Pseudomonas aeruginosa MIC METHOD	
Amikacin	<=2	Susceptible
Cefepime	2	Susceptible
Ceftazidime	2	Susceptible
Ciprofloxacin	<=0.25	Susceptible
Levofloxacin	1	Susceptible
Meropenem	<=0.25	Susceptible
Piperacillin-tazobactam	<=4	Susceptible
Tobramycin	<=1	Susceptible

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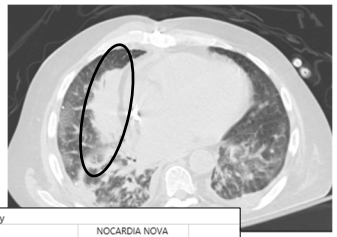
Pneumonia

- 45-year-old s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility

	NOCARDIA NOVA COMPLEX MIC METHOD	
.Comment	SEE NOTES	Note[1]
Amikacin		Susceptible
Amoxicillin + Clavulanate		Resistant
Ceftriaxone		Susceptible
Ciprofloxacin		Resistant
Clarithromycin		Susceptible
Doxycycline		Intermediate
Imipenem		Susceptible
Linezolid		Susceptible
Minocycline		Susceptible
Moxifloxacin		Resistant
Tobramycin		Resistant
Trimethoprim/sulfamethoxazole		Susceptible

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX

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Let's Switch to Parasites

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Toxoplasmosis

Epidemiology:
- 1988–1994 (NHANES III): ~22.5% of individuals aged 12-49 years were seropositive
- 1999–2000: seroprevalence decreased to 14.3%
- 2009–2010: Further decline to 10.1%

Syndromes seen after Transplant:
- Toxoplasma encephalitis
  - Headache, confusion to coma, seizures, focal neurologic deficits
- Pneumonitis (lung inflammation)
- Myocarditis (heart inflammation)
- Chorioretinitis

Diagnostics
- Serology is useful for risk assessment, not for diagnosing active disease
- **Toxoplasma PCR** on blood, CSF, BAL (bronchoalveolar lavage), or tissue
- Highly sensitive and specific for detecting T. gondii DNA

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Clinical Vignette

64-year-old man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant
- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram-negative rod bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

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Test Results

Strongyloides Antibody by ELISA: 100.00

INTERPRETATION: POSITIVE
- All reactions of <=1.7 units/ml should be considered NEGATIVE.
- All reactions >1.7 units/ml should be considered POSITIVE, indicative of infection with *Strongyloides stercoralis* at some indeterminate time.
- Sensitivity of the test is 93% and specificity is 98%.

Centers for Disease Control testing

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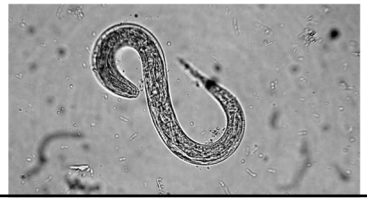
Strongyloides

- Nematode “roundworm”
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease



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The countries highlighted in **yellow** have sporadic endemicity, on the range of 1-3%. Those that are **orange** are endemic, while those that are **red** are generally hyperendemic, with the highest frequency of *Strongyloides* infection.

http://web.stanford.edu/group/parasites/ParaSites2006/Strongylodiasis/epidemiology.html

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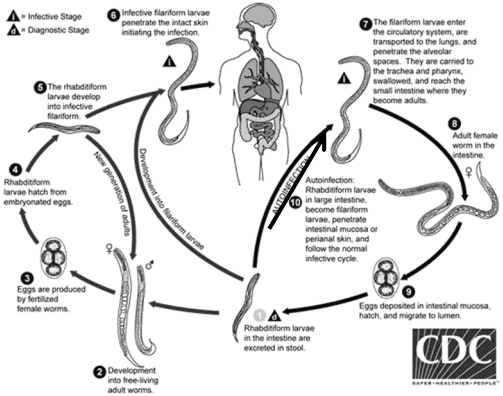
Strongyloides stercoralis Lifecycle



http://www.cdc.gov/dpdx/strongyloidiasis/

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Diagnostics Stewardship

Consider best methods to achieve most likely diagnosis; Hickam’s dictum* vs Occam‘s razor

The initial work up can be protocol driven; we have syndromic evaluations in the emergency room

Molecular diagnostics are superior but require us to be specific in our requests

- Multiplex (i.e., Biofire) helps

Non-invasive fungal diagnostics have been disappointing

- 1,3 beta D glucan, galactomannan (still love cryptococcal antigen!)
- serum *Mucorales* polymerase chain reaction is emerging

Toxoplasma PCR excellent example of sensitive and specific non-invasive test (rare diagnosis)

New technologies (i.e., cell free DNA testing) are emerging/interesting

The sooner we achieve a diagnosis, the sooner we can stop broad-spectrum antimicrobials & better outcomes for the patient

* Hickam's dictum is usually stated as "patients can have as many diseases as they damn (or darn) well please". This aphorism has been attributed to John Hickam (1914-1970) an American physician, who was Chair of the Department of Medicine at the University of Indiana

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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Rapid Diagnosis of Disseminated Tuberculosis Using Cell-Free DNA Sequencing in a Kidney Transplant Recipient, Transplantation 2023

Anna Apostolopoulou & Camille Nelson Kotton

- Middle aged kidney transplant recipient presented with fevers
- Extensive workup done
- "**On hospital day 13, while she remained febrile and without a definitive diagnosis, we sent a quantitative cfDNA test (Karius, Inc., Redwood City, CA). On HD 15, the Karius cfDNA test returned positive for M tuberculosis.**
- Subsequently, the mycobacterial blood, urine, and bronchoalveolar lavage cultures grew M tuberculosis on hospital days 17, 17, and 21, respectively). Bone cultures grew M tuberculosis 34 days after biopsy (after discharged from the hospital)."

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Drug Interactions: Transplant & Antimicrobials

- Azoles
  - Voriconazole, posaconazole > fluconazole
  - Isavuconazole – much less interaction
  - Increase tacrolimus (or cyclosporine, rapamycin)
- Rifamycins
  - Rifabutin < rifampin (=rifampicin)
  - Decrease tacrolimus (or cyclosporine, rapamycin)
  - Increase prednisone
- QT prolongation
  - Combination effect
  - May be present with liver disease
- Recommended: Use of on-line drug interaction calculator

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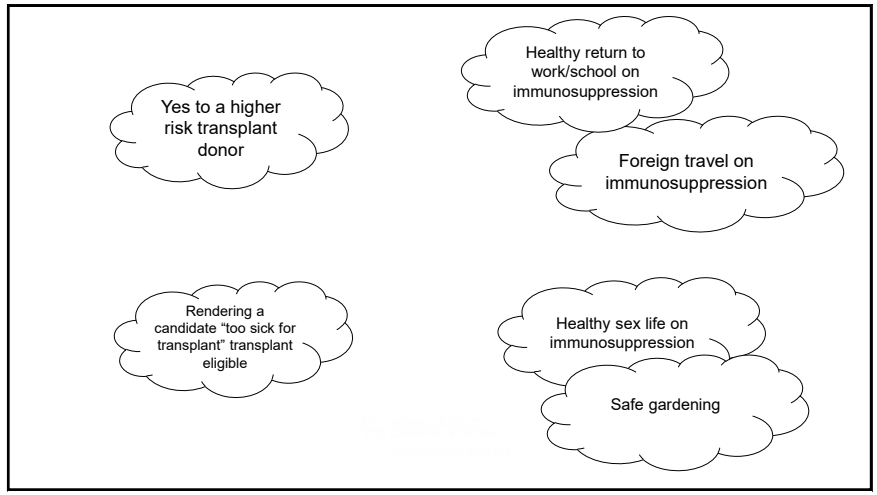

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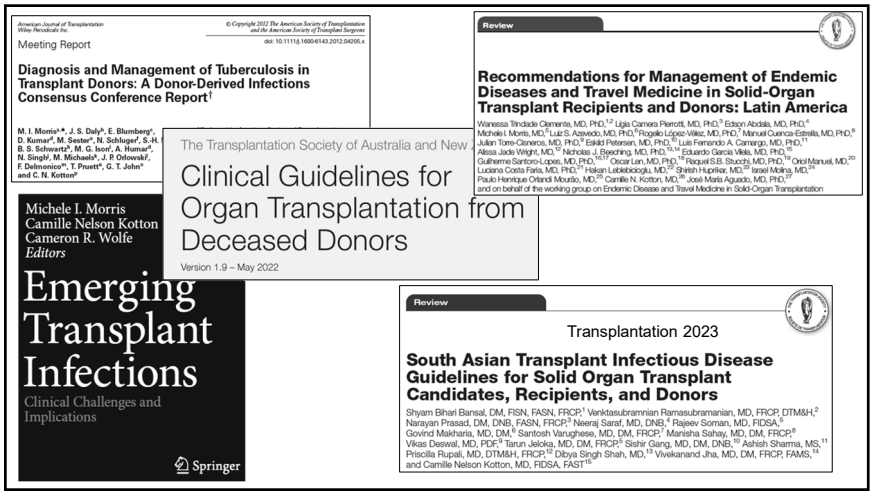

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Cardinal Rules 2025: Immunosuppression and Infection

1. Immunosuppression and infections not always straightforward
2. Be prepared to be surprised – think broadly
3. Prepare patient before immunosuppression – role for ID specialists
4. Prophylaxis & vaccines alter the risk equation
   - Primary and secondary prevention
5. Consider the source of infection: donor, recipient, blood products, geographic, more antibiotic resistance

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Online Only Lectures

OL4

Brain Abscess, Cavernous Sinus Thrombosis, and Subdural and Epidural Empyema

Allan Tunkel, MD

Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Allan R. Tunkel, MD, PhD, MACP

Professor of Medicine and Medical Science
The Warren Alpert Medical School of Brown University

7/23/2025

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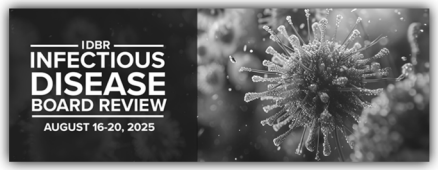

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Case #1

3

- 24-year-old female who presented with pain and swelling on the right side of her jaw that had been progressing over the last several weeks. She was unable to open her mouth. She denied fever or headache and had no past hospitalizations or illnesses. The patient had not been to the dentist within 10 years.
- T 99.8^{o}F, P 88, RR 14, BP 110/80
- Exam revealed swelling and erythema along her right mandible

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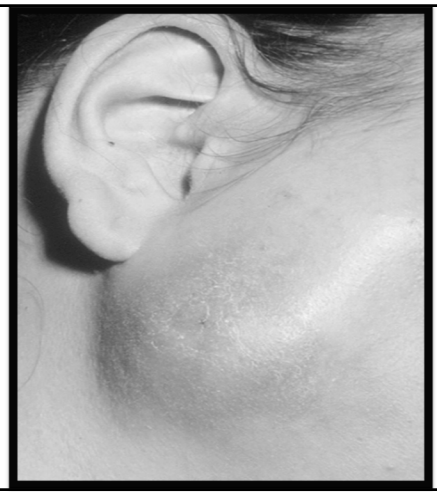

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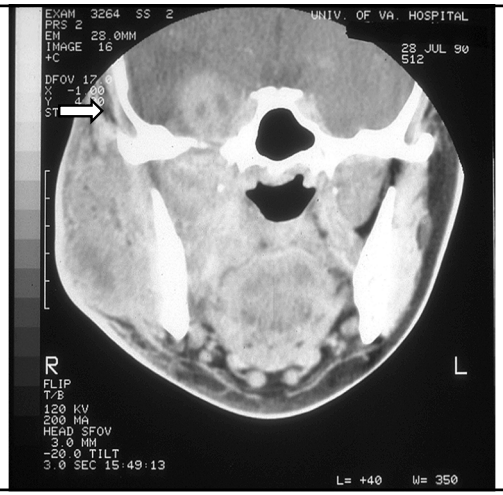
OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP



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Question #1

Which of the following empiric antimicrobial regimens should be initiated?

A. Ceftriaxone + metronidazole
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

6

Question #1

Which of the following empiric antimicrobial regimens should be initiated?

A. **Ceftriaxone + metronidazole ***
B. Vancomycin + cefepime
C. Trimethoprim-sulfamethoxazole
D. Voriconazole
E. Liposomal amphotericin B

7

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

8

Principles of Brain Abscess Management

9

- MR imaging is the diagnostic procedure of choice; diffusion-weighted imaging increases diagnostic accuracy (sensitivity and specificity 96% for differentiation from cancers [PPV 98%; NPV 92%])
- Lumbar puncture is contraindicated
- Biopsy or aspiration (via stereotactic guidance) is needed for microbiologic diagnosis
- Begin empiric antimicrobial therapy based on underlying condition and pathogenesis of spread of infection to brain

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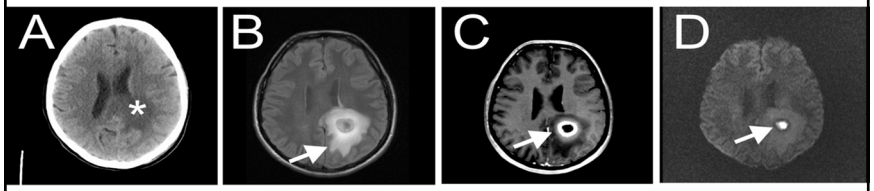

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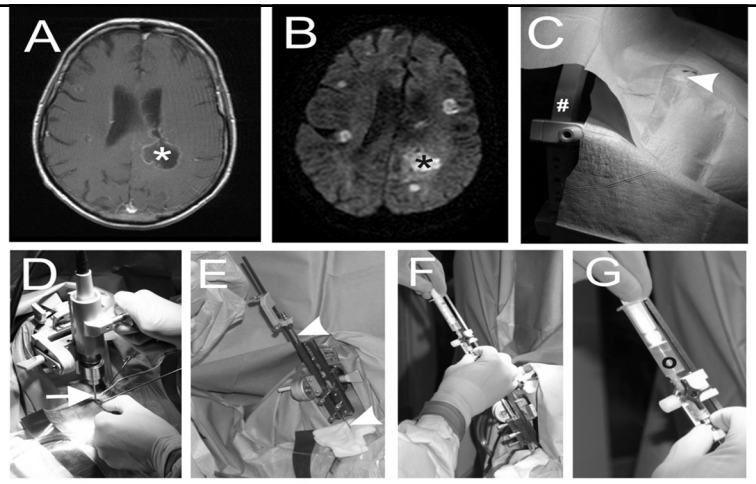

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Empiric Antimicrobial Therapy of Brain Abscess

12

Predisposing Condition	Antimicrobial Regimen
Otitis media or mastoiditis	Metronidazole + a third-generation cephalosporin[a]
Sinusitis	Vancomycin + metronidazole + a third-generation cephalosporin[a]
Dental sepsis	Third-generation cephalosporin[a] + metronidazole
Penetrating trauma or post-neurosurgical	Vancomycin + a third- or fourth-generation cephalosporin
Lung abscess, empyema, bronchiectasis	Vancomycin + metronidazole + a third- or fourth-generation cephalosporin + trimethoprim-sulfamethoxazole[b]
Bacterial endocarditis	Vancomycin[c]

[a]ceftriaxone or cefotaxime
[b]add if *Nocardia* suspected, along with 1-2 additional agents
[c]additional agents may be used based on other likely microbial etiologies

12

Empiric Antimicrobial Therapy of Brain Abscess

13

Predisposing Condition	Antimicrobial Regimen
Unknown	Vancomycin + metronidazole + a third or fourth generation cephalosporin; or vancomycin + meropenem
Transplant recipients	Add voriconazole + trimethoprim-sulfamethoxazole (plus additional 1-2 anti-nocardial agents) if *Nocardia* suspected
HIV-infected patients	Add pyrimethamine + sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol for possible tuberculosis

13

Case #2

14

- 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

14

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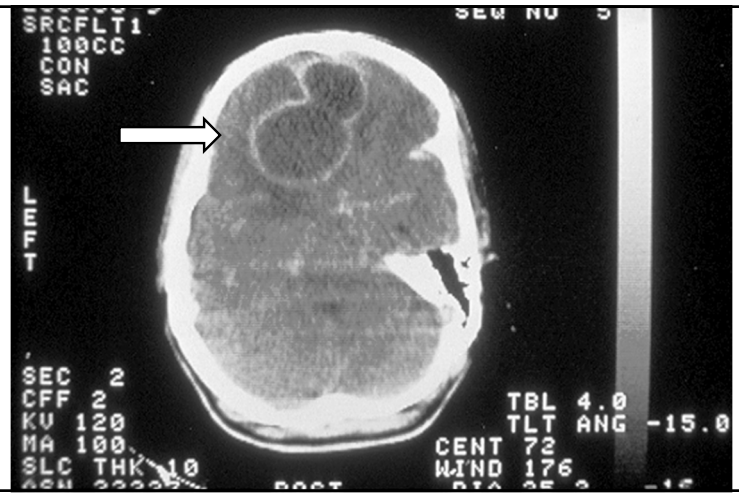

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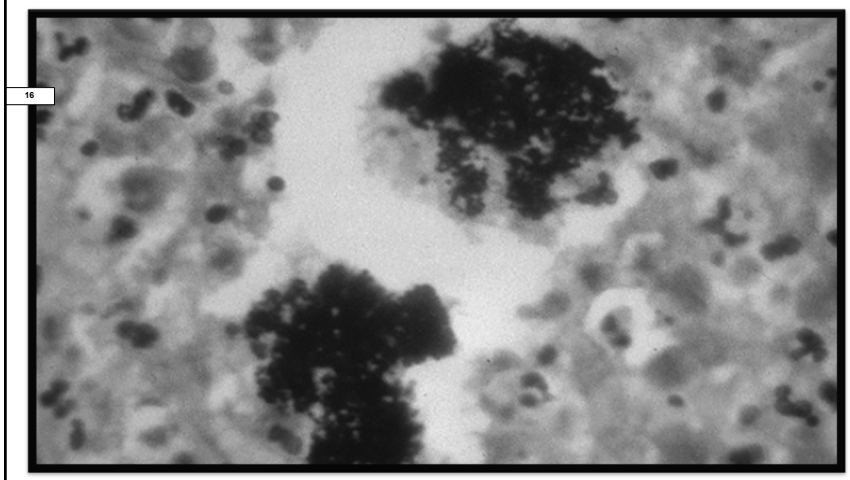

16

OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP

Case #3

17

- 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

17

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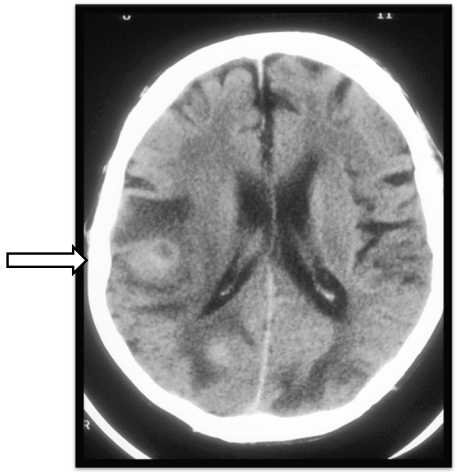

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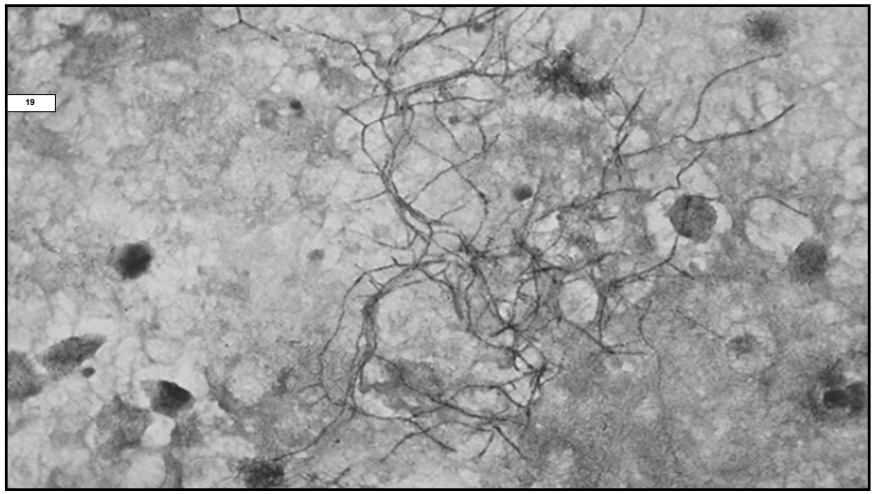

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Question #2 (Case #3)

20

Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. Trimethoprim-sulfamethoxazole + imipenem
C. Daptomycin + cefepime
D. Liposomal amphotericin B + 5-FC
E. Voriconazole

20

Question #2 (Case #3)

21

Which of the following antimicrobial regimens should be initiated?

A. Penicillin + metronidazole
B. **Trimethoprim-sulfamethoxazole + imipenem ***
C. Daptomycin + cefepime
D. Liposomal amphotericin B + 5-FC
E. Voriconazole

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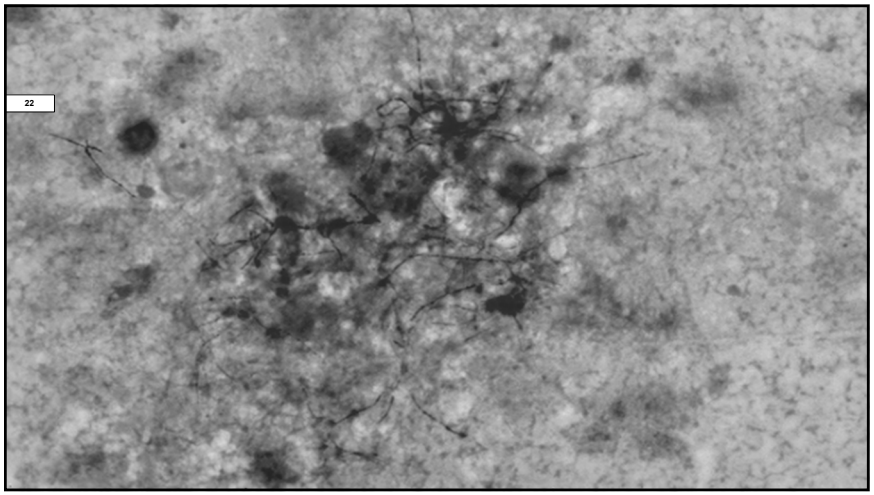

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Case #4

23

- 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

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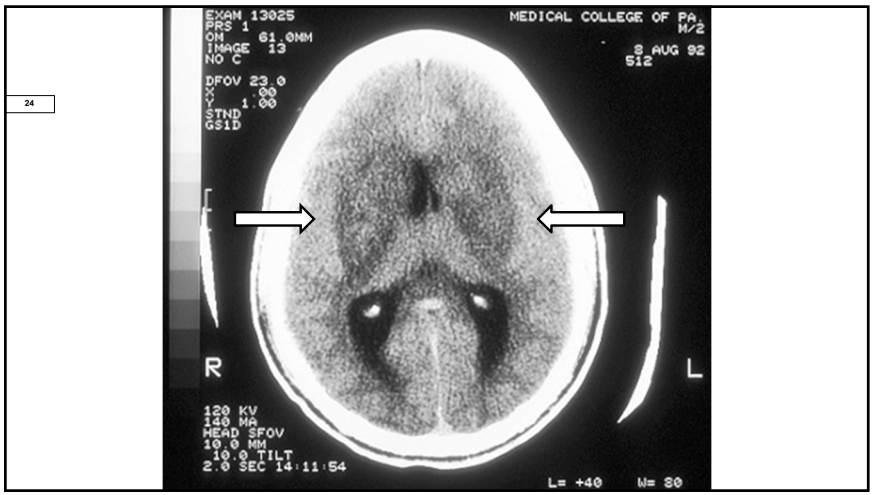
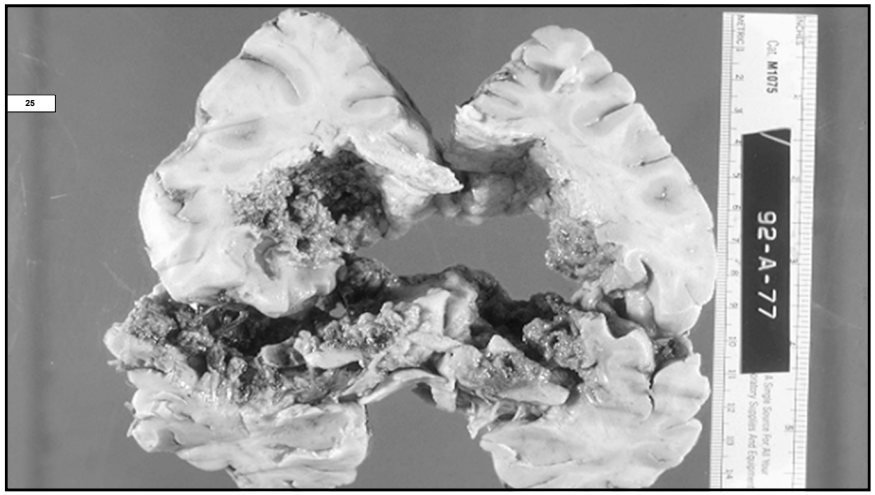


24

OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP



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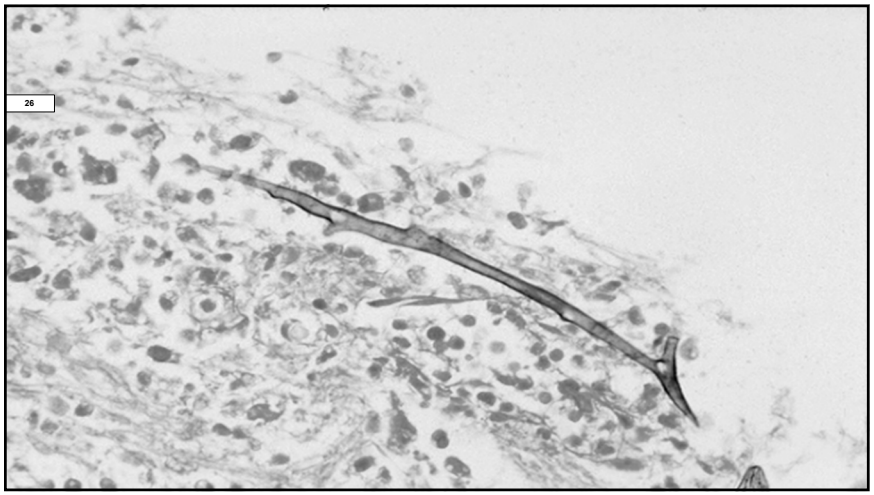

26

Case #5

27

- 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

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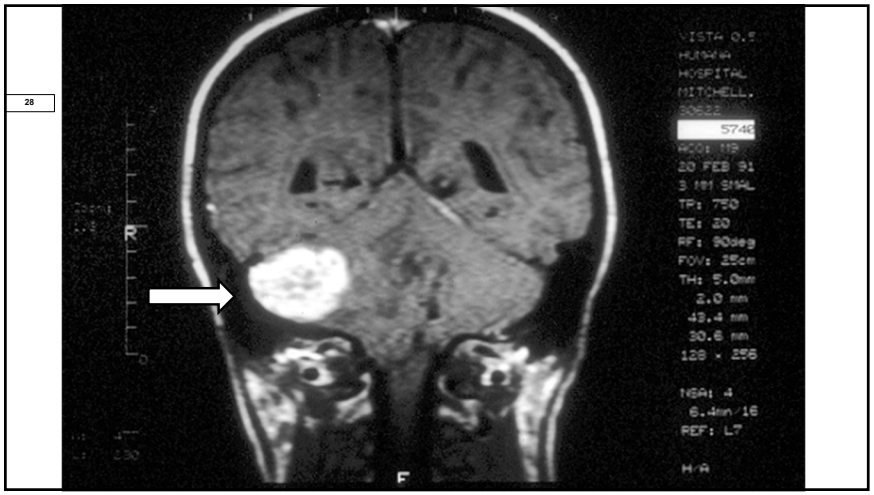
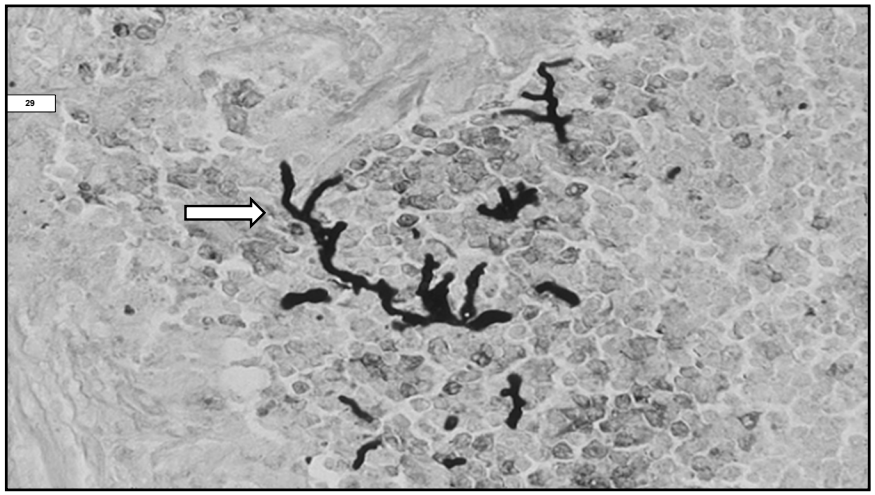


28

OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP



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Case #6

30

- 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

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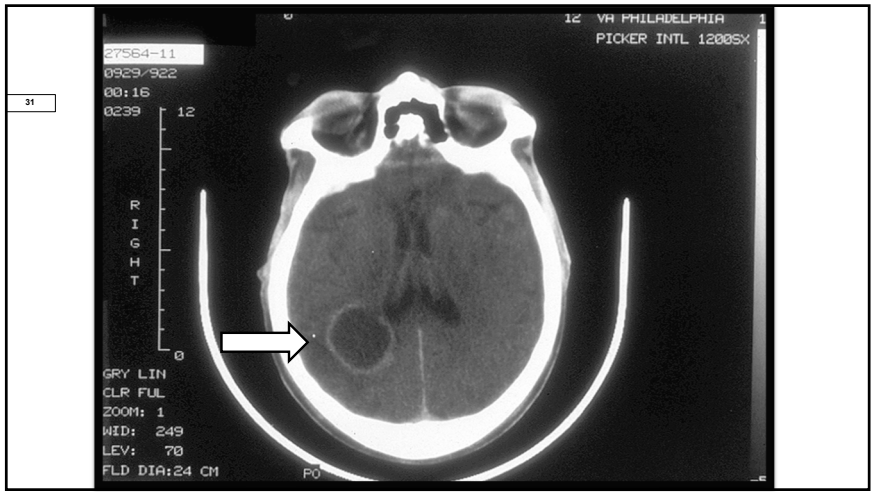

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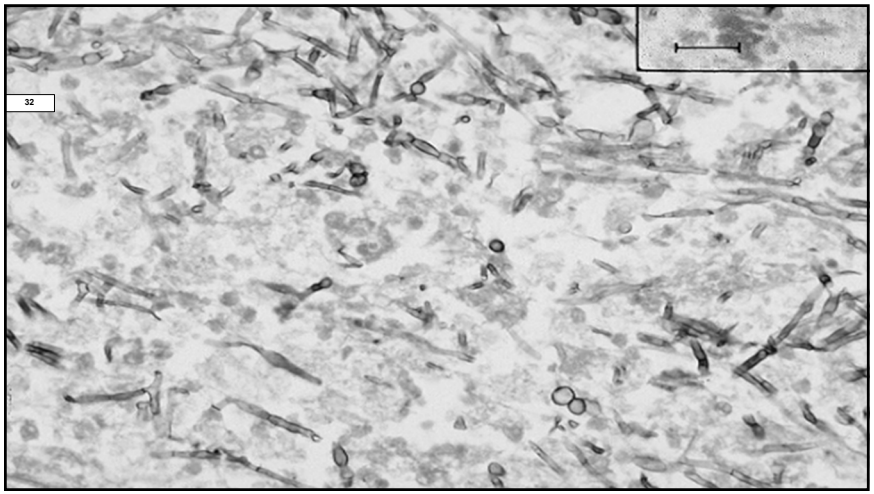

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OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP

Principles of Brain Abscess Management

33

- 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

33

Antimicrobial Therapy of Brain Abscess

34

Organism	Antimicrobial Therapy
Actinomyces sp.[a]	Penicillin G
Bacteroides fragilis[a]	Metronidazole
Enterobacterales[a]	Third- or fourth-generation cephalosporin, or another agent based on in vitro susceptibility
Fusobacterium sp.[a]	Metronidazole
Pseudomonas aeruginosa	Ceftazidime or cefepime or meropenem
Staphylococcus aureus	Nafcillin, oxacillin, or vancomycin
Strep. milleri;[a] other streptococci[a]	Penicillin G

[a]depending on pathogenesis of infection, may be isolated as part of a mixed infection

34

Antimicrobial Therapy of Brain Abscess

35

Organism	Antimicrobial Therapy
Nocardia asteroides	Trimethoprim-sulfamethoxazole + imipenem; add third drug in those with severe disease, or those failing standard therapy
Mycobacterium tuberculosis	Isoniazid + rifampin + pyrazinamide ± ethambutol

35

Antimicrobial Therapy of Brain Abscess

36

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

36

Case #7

37

- 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

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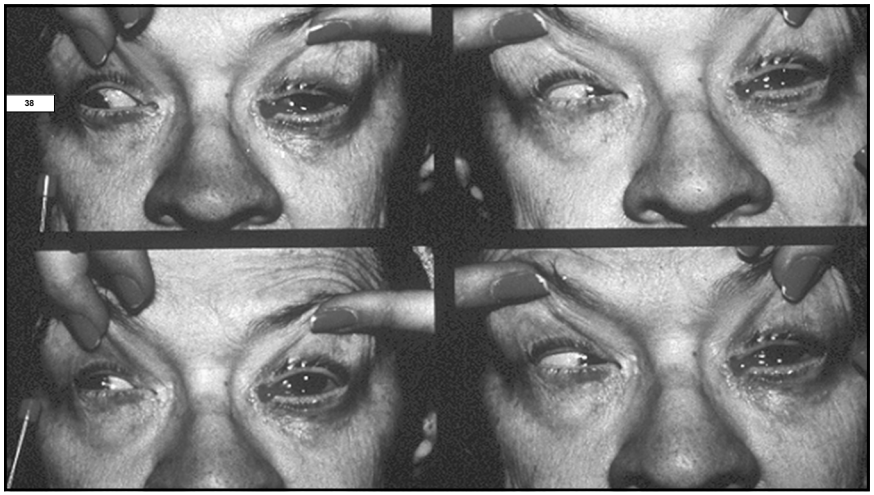

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Question #3 (Case #7)

39

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

39

Question #3 (Case #7)

40

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

40

Epidemiology and Etiology of Septic Cavernous Sinus Thrombosis

41

Risk Factors	Etiologic Agents
Paranasal sinusitis	Staphylococci (60-70%)
Facial infection	Streptococci (~17%)
Dental infection	Gram-negative bacilli (~5%)
	Pneumococci (~5%)
	Bacteroides sp. (~2%)

41

Clinical Features of Septic Cavernous Sinus Thrombosis

42

Symptoms	Signs
Headache (52%)	Periorbital edema (73%)
Facial pain	Chemosis
Vision loss	Papillitis
Fever	Oculomotor palsies
Double vision	Proptosis

42

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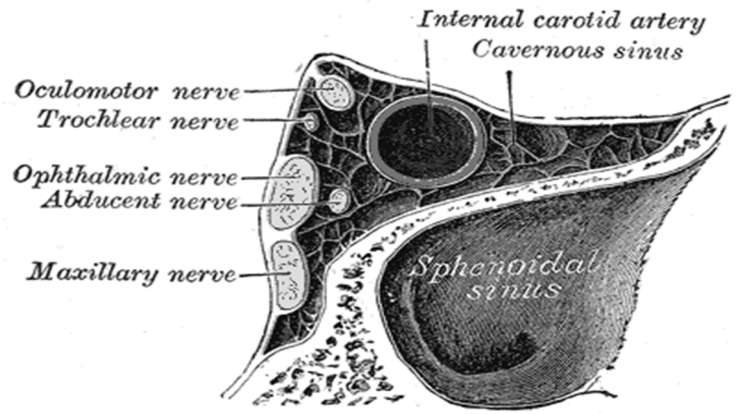

Tunkel AR. Principles and Practice of Infectious Diseases, 8th ed. 2015.

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Radiologic Findings lin Septic Cavernous Sinus Thrombosis

44

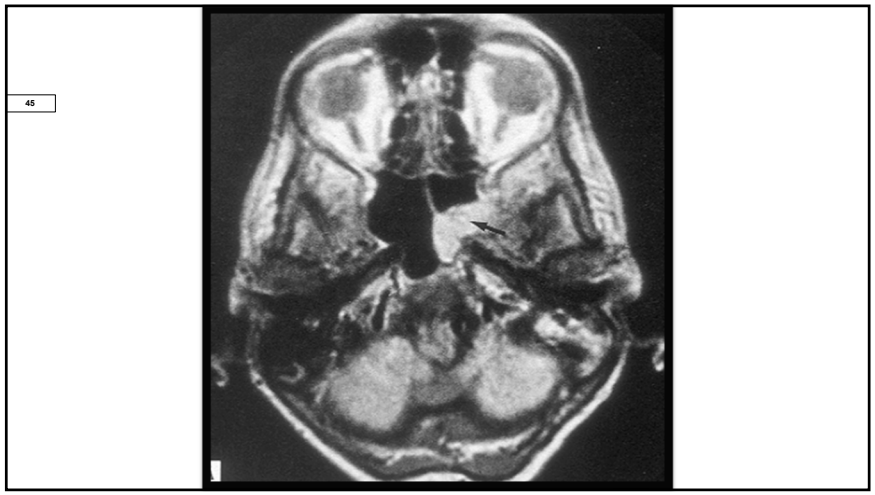
MR imaging

- Noninvasive diagnostic procedure of choice
- MRA and MRV can directly visualize cerebral vasculature
- Fullness in cavernous sinus region
- Paranasal sinus fluid

44

OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP



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Management of Septic Cavernous Sinus Thrombosis

- Culture and drainage of infected sinuses
- Antimicrobial therapy (vancomycin + metronidazole + 3rd or 4th generation cephalosporin)
- Anticoagulation - Yes
- Corticosteroids - No

46

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 102º F and he is lethargic
- Laboratory studies normal

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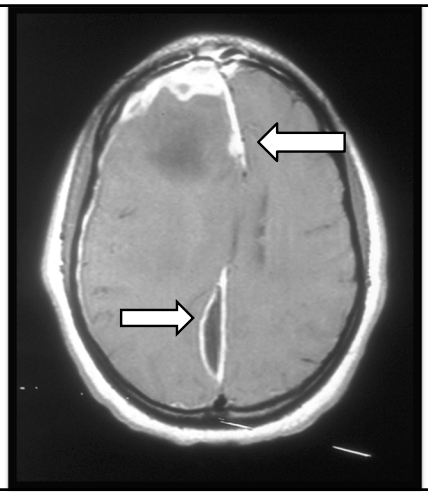

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OL4 Brain Abscess, Cavernous Sinus Thrombosis, Subdural Empyema, and Epidural Abscess

Speaker: Allan Tunkel, MD, PhD, MACP

Question #4 (Case #8)

49

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

49

Question #4 (Case #8)

50

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 ***

50

Cranial Subdural Empyema and Cranial Epidural Abscess

51

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%)

51

Cranial Subdural Empyema and Cranial Epidural Abscess

52

Subdural Empyema
(acute course)

- Fever
- Headache
- Depressed consciousness
- Hemiparesis
- Seizures
- Nuchal rigidity
- Gaze palsies/ataxia

Epidural Abscess
(indolent course)

- Headache
- Fever
- Seizures
- Focal neurologic signs
- Altered mental state

52

Principles of Management of Cranial Subdural Empyema

53

- 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

53

Surgical Management of Cranial Subdural Empyema

54

Surgical Procedure	Mortality Rate
Burr hole(s)	23.3%
Craniectomy	11.5%
Craniotomy	8.4%

Nathoo et al. Neurosurgery 2001;49:872

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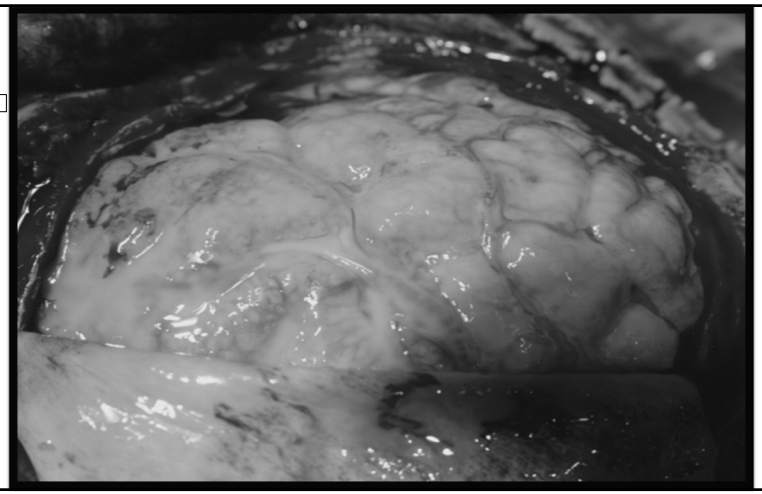

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Epidemiology of Spinal Epidural Abscess

56

- 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

56

Etiology of Spinal Epidural Abscess

57

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

57

Clinical Stages of Spinal Epidural Abscess

58

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

58

Principles of Management of Spinal Epidural Abscess

59

- 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 (i.e., vancomycin) and coverage for gram-negative bacilli

59

Principles of Management of Spinal Epidural Abscess

60

- 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

60

61

Questions

Allan R. Tunkel, MD, PhD, MACP
Email: allan_tunkel@brown.edu

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Online Only Lectures

OL5

Infections of Upper and Lower Urinary Tract

Barbara Trautner, MD

Urinary Tract Infections

Barbara Trautner, MD, PhD

Professor of Medicine
Baylor College of Medicine
Houston, Texas

7/23/2025

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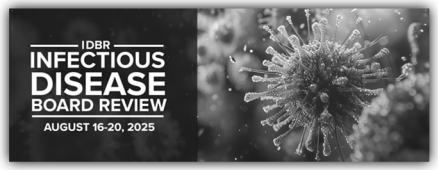


Disclosures of Financial Relationships with Relevant Commercial Interests

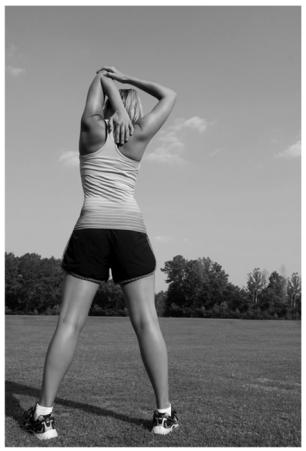
- **Current:** Shionogi (COVID trial)
- **Past:** Genentech, Pfizer, Abbvie, Abbott Laboratories, Bristol Myers Squibb, Phiogen, Peptilogics

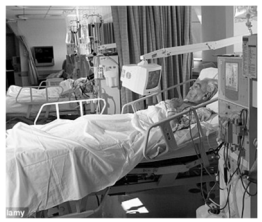
2

Topics to Cover

- Acute cystitis in women
- Recurrent cystitis in women
- Asymptomatic bacteriuria
- Catheter-associated UTI
- Pyelonephritis
- Urosepsis and worse

3





UTI Differs in Different Populations

UTI is not the same entity in these different populations

4

The Great Divide

My patient populations

- Men
- Older adults in long-term care
- Persons who require urinary catheters for bladder drainage
- Persons with neurogenic bladders

UTI treatment evidence base

- Pre-menopausal women
- Female college students and university staff

5

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. TMP/SMX
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

6

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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. 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 does not prevent pyelonephritis

hpf, high-powered field; TMP/SMX, trimethoprim/sulfamethoxazole

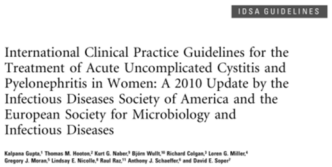
7

Current Infectious Diseases Society of America (IDSA) UTI Guidelines*

*Complicated UTI guidelines coming soon

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

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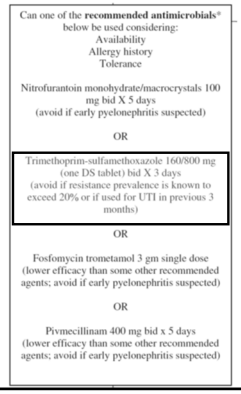
IDSA Cystitis Guidelines (2010)

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)

bid, twice daily; DS, double strength

9

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

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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

GFR, glomerular filtration rate

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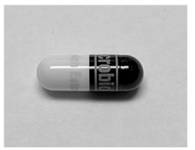
Nitrofurantoin Adverse Events



- Pulmonary toxicity – RARE
  - Acute: reversible hypersensitivity reaction
  - Subacute or chronic: diffuse pneumonitis
    - 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

QID, four times daily

Santos, JAGS 2016, PMID: 27100576

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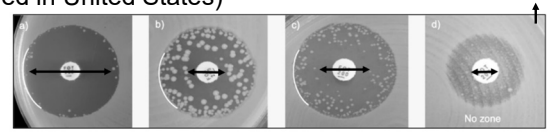
Fosfomycin: Clinical Use for UTI

- High levels in urine for over 24 hours
- Single 3 gm dose for cystitis
- Developing niche for ESBL- and KPC- Enterobacterales
  - 3gm every 48-72 hours
- IV fosfomycin associated with hypokalemia and elevated LFTs (not approved in United States)



Photos from eucast.org; arrows (↔) reflect CLSI recommendations

CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; IV, intravenous; KPC, Klebsiella pneumoniae carbapenemase; LFT, liver function tests

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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.

C. diff, Clostridioides difficile

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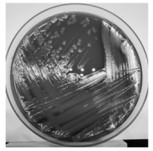
New Oral Drugs for Cystitis: FDA Approved for Uncomplicated UTI

- Pivmecillinam
  - Pro-drug of mecillinam
  - Binds to PBP-2 in Gram-negative cell wall
  - Effective against ESBL +Enterobacterales, Staph saprophyticus
- Gepotidacin
  - Blocks DNA topoisomerase
  - Effective against ESBL+ Enterobacterales, S. saprophyticus, and E. faecalis
  - Diarrhea as a side effect
- Sulopenem
  - Thiopenem – new beta-lactam class
  - Effective against ESBL+ Enterobacterales, S. saprophyticus
  - Did not get approval for complicated UTI



Not for *Pseudomonas* or VRE

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Question #2

A 38-year-old woman comes in for recurrent UTI. This is her 3rd episode of symptomatic, culture-proven cystitis in the past 12 months. The recurrent UTIs are very inconvenient to her. She notes that her UTI symptoms usually begin within 2 days of sexual intercourse.

You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

A. Nitrofurantoin daily for 24 months
B. Nitrofurantoin one dose after intercourse for 6 months
C. Ciprofloxacin daily for 6 months
D. Trimethoprim-sulfamethoxazole twice daily for 6 months
E. Cranberry tablets

16

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You offer an antibiotic prescription to allow her to self-treat when she feels the cystitis symptoms developing, but she travels internationally and would rather completely avoid developing a UTI.

Which of the following is the most appropriate strategy to prevent recurrent UTI in this woman?

A. Nitrofurantoin daily for 24 months – duration usually 3-6 months
B. Nitrofurantoin one dose after intercourse for 6 months – use antibiotics specifically after her trigger situations
C. Ciprofloxacin daily for 6 months – not a good drug for prophylaxis
D. Trimethoprim-sulfamethoxazole twice daily for 6 months – dose is too high
E. Cranberry tablets – minimal data to support

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Prevention and Management of Recurrent UTI

- Self-treatment coupled with urine collection for culture is an appropriate strategy
- Use the most focused antibiotic and as sparingly as possible
- If the woman's episodes are related to sexual intercourse, one dose of antibiotics after intercourse is an effective strategy
- Guidelines suggest treating daily for 3-12 months
- No clarity on which antibiotic to use, other than to avoid fluoroquinolones given side effects and resistance

Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline (2022)
https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti

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Non-antibiotic Strategies to Prevent Recurrent UTI

Likely helpful (FDA approved)
- Increasing fluid intake
- Vaginal estrogen in post-menopausal women
- Methenamine (?)

Uncertain benefit (not FDA approved)
- Other behavioral changes
- Cranberry products (?)
- D-mannose
- Probiotics
- Other supplement (liquid or other)

Fluid intake: Hooton TM, et al. *JAMA Intern Med*. 2018
Methenamine trials: Harding C, et al. *Health Technol Assess*. 2022
Botros C, et al. *Int Urogynecol J*. 2022
Systematic review of cranberry products: Williams G, et al. *Cochrane Database Syst Rev*. 2023

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Question #3

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 hypertension and type 2 diabetes mellitus.

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

BMI, body mass index

20

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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 – this is a case of asymptomatic bacteriuria

BMI, body mass index

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Prevalence of Asymptomatic Bacteriuria

Population	Prevalence, %
Children	
Boys	<1
Girls	1–2
Healthy women	
Premenopausal	1.0–5.0
Pregnant	1.9–9.5
Postmenopausal (age 50–70 y)	2.8–8.6
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	23–69
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

mo, month; y, year

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

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Choosing Wisely®
An initiative of the ABIM Foundation

IDSA
Infectious Diseases Society of America

Five Things Physicians and Patients Should Question

Don't treat asymptomatic bacteruria with antibiotics.

Inappropriate use of antibiotics to treat asymptomatic bacteruria (ASB), or a significant number of bacteria in the urine that occurs without symptoms such as burning or frequent urination, is a major contributor to antibiotic overuse in patients. With the exception of pregnant patients, patients undergoing prostate surgery or other invasive urological surgery, and kidney or kidney pancreas organ transplant patients within the first year of receiving the transplant, use of antibiotics to treat ASB is not clinically beneficial and does not improve morbidity or mortality. The presence of a urinary catheter increases the risk of bacteruria, however, antibiotic use does not decrease the incidence of symptomatic catheter-associated urinary tract infection (CAUTI), and unless there are symptoms referable to the urinary tract or symptoms with no identifiable cause, catheter-associated asymptomatic bacteruria (CA-ASB) does not require screening and antibiotic therapy. The overtreatment of ASB with antibiotics is not only costly, but can lead to C. difficile infection and the emergence of resistant pathogens, raising issues of patient safety and quality.

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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

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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

CTFPHC, Canadian Task Force on Preventive Health Care; USPSTF, United States Preventive Services Task Force

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Myth-Busting (True Facts!)

- Bacteriuria ≠ UTI
  - Bacteriuria in the urine can be bladder colonization **or** symptomatic urinary tract infection
- Pyuria ≠ UTI
  - The presence of WBC in the urine doesn't help much with diagnosis of UTI
  - Absence of pyuria suggests to look for a non-UTI diagnosis
- Foul smelling urine ≠ UTI
- Sediment or cloudy urine in catheter tubing ≠ UTI
  - All catheterized bladders develop high level bacteriuria
  - Flushing the catheter to make sure it is patent is a good idea
- Healthy bladders are not sterile in many people
- Take home points:
  - Order urine tests only in patients with urinary symptoms
  - The best thing you can do with asymptomatic bacteriuria is leave it alone
  - Pyuria is not a reliable marker for UTI
  - Changes in the urine are not reliable markers for UTI

WBC, white blood cell

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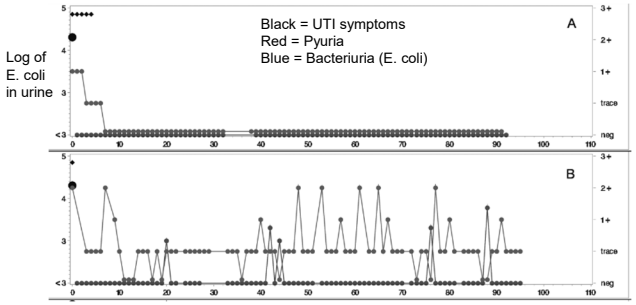
Pyuria Not Very Predictive (Even in Non-catheterized Women)



Leukocyte esterase on dipstick

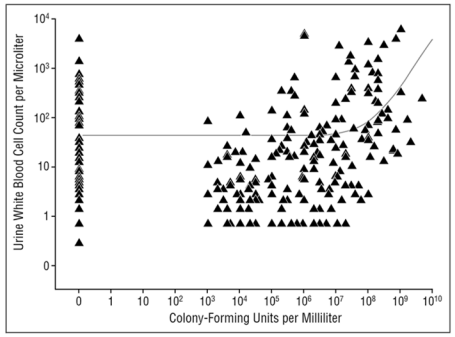
104 women followed for 3 months each with daily urine testing

Overall, the PPV (positive predictive value) of pyuria for *E. coli* bacteriuria was 4%

Hooton et al., Clin Infect Dis. 2021 Apr 26;72(8):1332-1338[28]

28

Relationship Between Pyuria and Bacteriuria/Candiduria in Catheterized Patients



1,497 newly catheterized patients followed daily with urine testing and symptom diaries

235 developed bacteriuria with at least 1,000 CFU/mL

No significant differences in fever or urinary symptoms between patients who did/did not develop bacteriuria

No correlation between pyuria and bacteriuria (flat line) until colony counts are over 10^8

Tambyah and Maki, Arch Intern Med. 2000 Mar 13;160(5):678-82 and 673-7
CFU, colony-forming unit

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Question #4

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

30

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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 – will breach the mucosa, and bacteriuria would contaminate the surgical field
B. Diabetes mellitus – no, see ASB guidelines
C. Kidney transplant – not necessary to treat ASB after >1 month post transplant
D. Knee prosthesis placement – not fully addressed in the 2019 ASB guidelines

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Question #5

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

32

Question #5

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
   - Ineffective

B. Routine catheter change every 3 days
   - Ineffective

C. Screening for and treatment of bacteriuria
   - Ineffective AND confers excess antibiotic use

D. Keeping the collecting bag below the level of the bladder
   - **Gravity helps prevent reflux to the kidneys**

E. Use of antiseptic- or antibiotic-coated urinary catheters
   - Minimal impact and approved only for short-term use

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Question #6

A 37-year-old woman with a history of recurrent UTIs developed typical symptoms of urgency, frequency, and dysuria five days ago. On the advice of her close friend, she decided to treat this UTI with a nutritional supplement instead of antibiotics. Symptoms did not resolve, and she developed worsening low back pain. This morning, she vomited once. In the office, her temperature is 100.5F, BP 135/70, HR 110, RR 16. She is not currently vomiting and can sip water.

You do not have any prior urine cultures to guide your therapy. She took some antibiotics for UTI 3 months ago but doesn't know what she took.

Assuming you can manage her as an outpatient, what empiric treatment would you offer?

A. Oral trimethoprim-sulfamethoxazole
B. Oral ciprofloxacin
C. One dose of ceftriaxone or gentamicin followed by oral ciprofloxacin
D. Cephalexin
E. Nitrofurantoin

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

34

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Assuming you can manage her as an outpatient, what empiric treatment would you offer?

A. Oral trimethoprim-sulfamethoxazole
B. Oral ciprofloxacin
C. One dose of ceftriaxone or gentamicin followed by oral ciprofloxacin – safest empiric options without cultures to guide you and with known prior antibiotic exposure
D. Cephalexin
E. Nitrofurantoin

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

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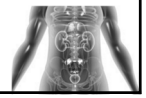
Management of Pyelonephritis

- Many clinical trials included pyelonephritis with complicated UTI
- Complicated UTI increasingly means urinary tract infection that has spread beyond the bladder (to kidneys, bloodstream)
- Empiric oral therapy
  - Trimethoprim-sulfamethoxazole 7 days
  - Fluroquinolones 5-7 days
  - Consider a one-time dose of IM ceftriaxone or gentamicin while awaiting cultures
  - Oral beta-lactams (cephalosporins, amoxicillin-clavulanate)
- Empiric intravenous therapy
  - Cephalosporins, piperacillin-tazobactam, carbapenems, fluoroquinolones
- To avoid: nitrofurantoin and fosfomycin



Johnson and Russo, NEJM 2018. 378;1

36

Case #7

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

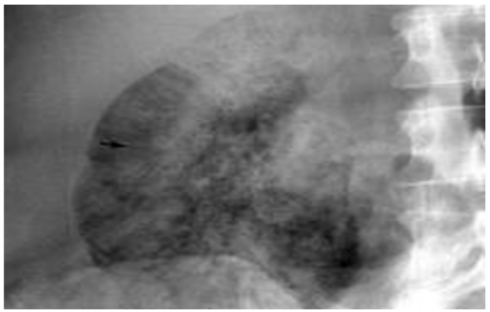
Troponin 7.2, EKG with ST elevations; HgB A1c 10.5

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.

37

Question #7



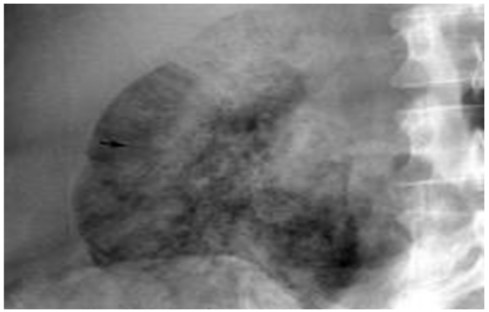
X-ray of Abdomen

What would you order next?

A. Abdominal ultrasound
B. Abdominal CT
C. Nasogastric tube
D. Stool for *C. diff* testing

38

Question #7



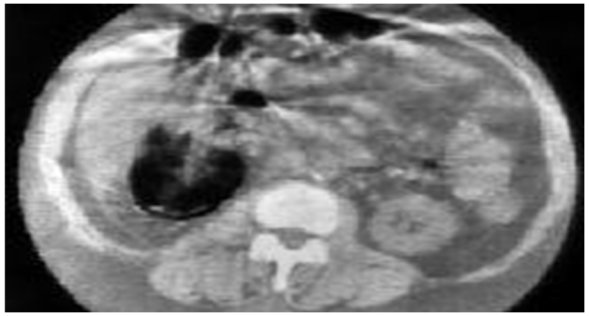
X-ray of Abdomen

What would you order next?

A. Abdominal ultrasound
B. Abdominal CT – You are looking at gas in the kidney
C. Nasogastric tube
D. Stool for *C. diff* testing

39

Abdominal CT with Emphysematous Pyelonephritis



CT showing gas within the renal parenchyma

40

Clinical Course of Case #7

- 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 coronary artery bypass surgery

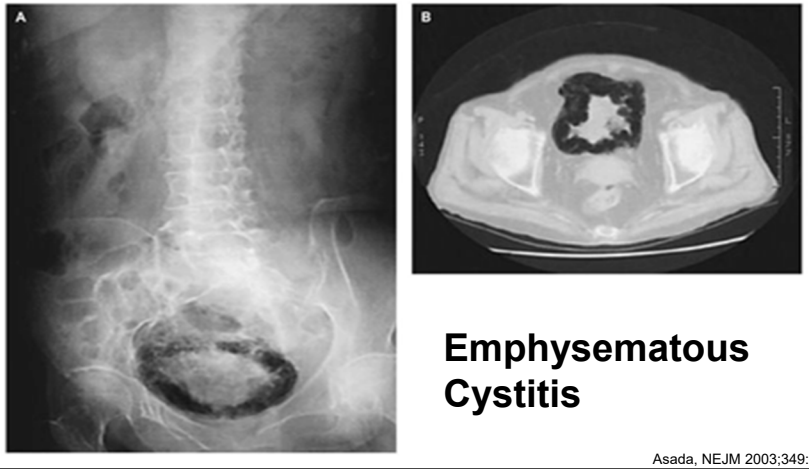
41

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

42



Emphysematous Cystitis

Asada, NEJM 2003;349: 258

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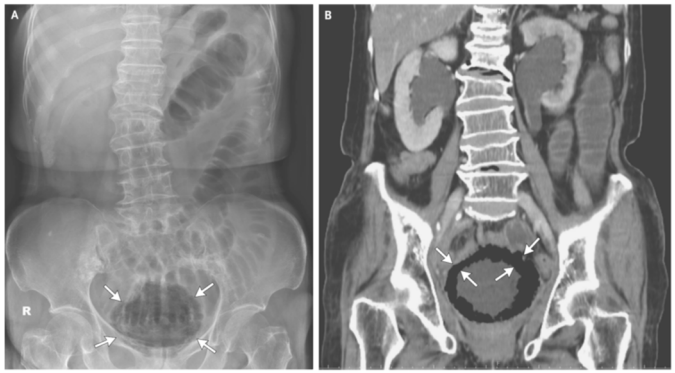

Tzou, NEJM 2016: 375; 18

44

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**

45

Question #8

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

46

Question #8

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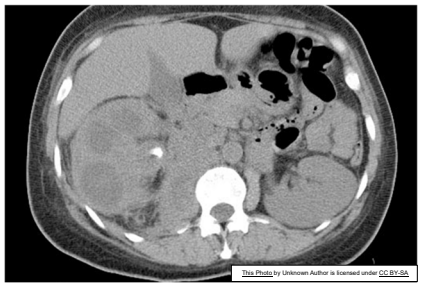
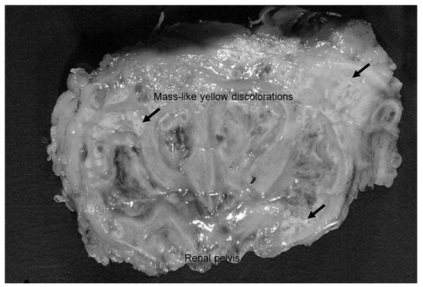
In addition to CT scan, what will be the definitive therapy?

A. Renal biopsy
B. 3-6 months of antibiotics based on current urine culture
C. Percutaneous drainage
D. **Nephrectomy – Can you name the diagnosis?**

47



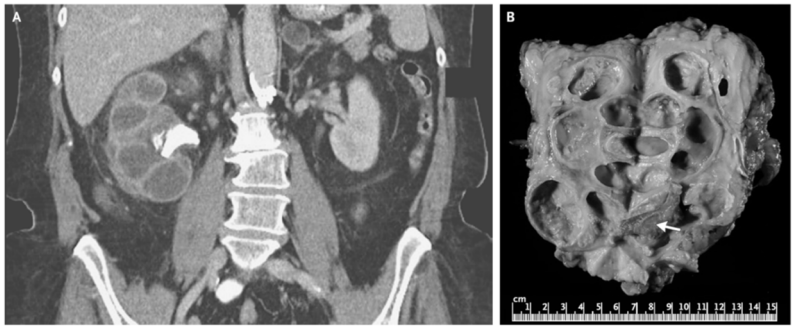


Xanthogranulomatous Pyelonephritis

https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

48

Xanthogranulomatous Pyelonephritis



Bear Paw Sign

Marinacci, New England Journal of Medicine 2018; 378:10

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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

50

To Re-Cap

- Acute and recurrent cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnant women-screen and treat
  - Urologic surgery – screen and treat
  - Everyone else – don't test the urine
- Catheter-associated UTI – ensure drainage
- Pyelonephritis – treat with tissue-active agent
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

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Is Everything Clear Now?

- trautner@bcm.edu
- @bwtrautner

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Online Only Lectures

OL6

HIV-Associated Opportunistic Infections III

Rajesh Gandhi, MD

HIV-Associated Opportunistic Infections (OI): Part 3

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

Acknowledgement: Dr. Henry Masur for sharing slides

7/23/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

HIV Associated Opportunistic Infections: Part 3

Mucocutaneous Infections: Candida, VZV, HSV, EBV

Fungal Infections (other than Cryptococcal Meningitis and Candida)

Gastrointestinal (GI) Complications

Cytomegalovirus (CMV)

3

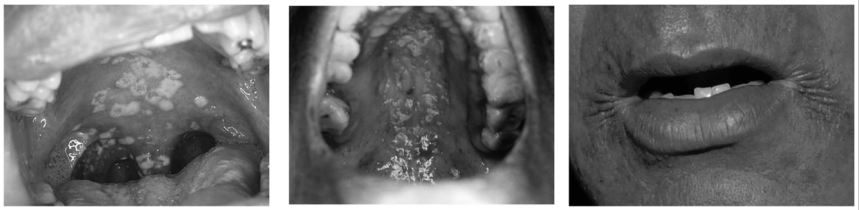
Mucocutaneous Candidiasis in PWH

- Oropharyngeal and esophageal candidiasis common in people with HIV (PWH) who have CD4 cell counts <200
  - Esophageal candidiasis typically occurs at lower CD4 counts than oropharyngeal candidiasis
- Mostly due to *Candida albicans*
- Invasive candidiasis is **NOT** HIV related
  - Candida in blood should raise suspicion of catheter related blood stream infection or injection drug use

4

Oropharyngeal Candidiasis

Pseudomembranous **Erythematous** **Angular cheilosis**

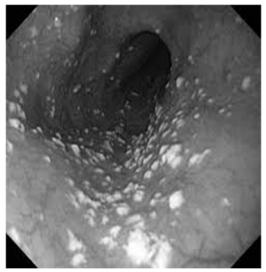


Photograph from
David H. Spach, MD

https://www.hiv.uw.edu/go/basic-primary-care/oral-manifestations/core-concept/all
Also: Drs. Anisa Mosam, Richard Johnson. Patil S et al, Front Microb, 2015

5

Esophageal Candidiasis



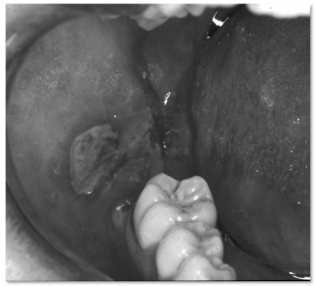
6

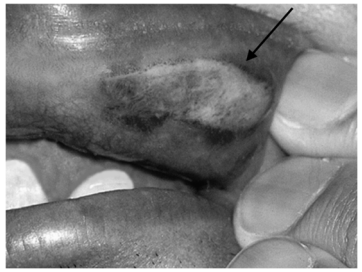
Mucocutaneous Candidiasis in PWH: Management

- Fluconazole primary prophylaxis or chronic suppression NOT RECOMMENDED
- Treatment:
  - Oral candidiasis: oral fluconazole 100 to 200 mg daily (except during pregnancy); topical miconazole, clotrimazole troches, nystatin
  - Esophageal candidiasis: fluconazole, 14-21 days

7

Aphthous Ulcers





Black arrow points to a large aphthous lesion on the lip.
Photograph from David H. Spach, MD

https://www.hiv.uw.edu/go/basic-primary-care/oral-manifestations/core-concept/all
Additional images courtesy of Drs. Anisa Mosam, Richard Johnson and Medscape

8

Causes of Odynophagia in People with Advanced HIV

- Esophageal candidiasis
- Giant aphthous ulcers
- HSV esophagitis
- CMV esophagitis

9

Herpes Zoster

- **Pre ART**
  - 15-fold higher incidence of zoster than general population!
- **Post ART**
  - Still increased risk even on suppressive ART
- **Localized (dermatomal)**
  - May occur at all CD4 cell counts
    - More frequent when CD4 cell count <200 or HIV RNA not suppressed
  - Risk of zoster increased in the months after ART initiation, possibly because of immune reconstitution inflammatory syndrome-related mechanism.

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

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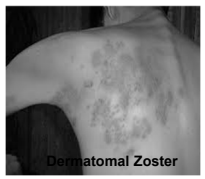
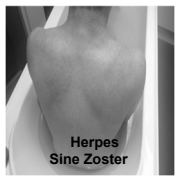
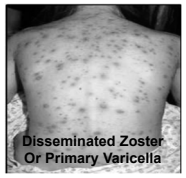
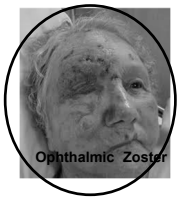
Localized and Disseminated Herpes Zoster



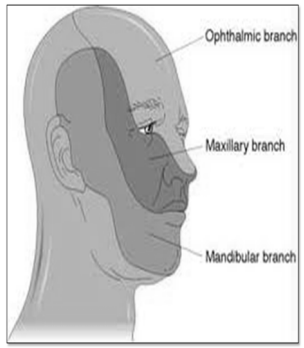


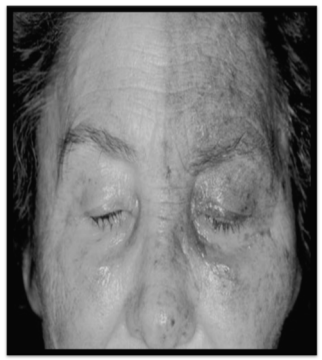




11

Zoster Ophthalmicus
Ophthalmic Branch CN V

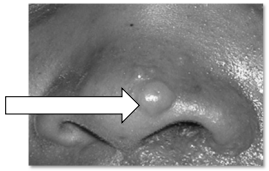


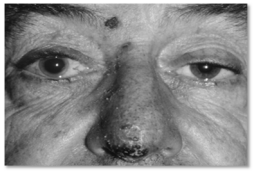


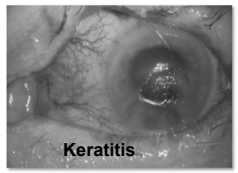
12

Hutchinson's Sign As Precursor to VZV Eye Disease

(Nasociliary Nerve of Ophthalmic Branch CN V)







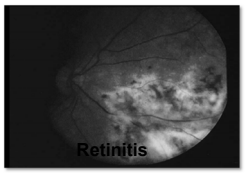


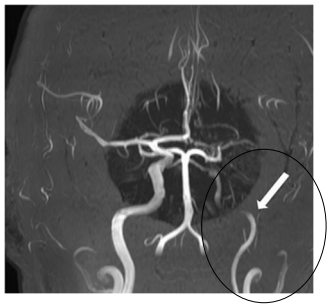
Image C. Stephen Foster, MD, Massachusetts Eye Research and Surgery Institute

- Vesicles on tip of nose, or vesicles on side of nose
- Accompanies development of ocular manifestations: keratitis, anterior uveitis

13

Zoster Ophthalmicus Related Stroke

- Vascular inflammation and occlusion
- Days or months post zoster (median 4 months)
- Occasionally cutaneous lesions absent (33%)
- Diagnosis: PCR of CSF or VZV antibody production in CSF

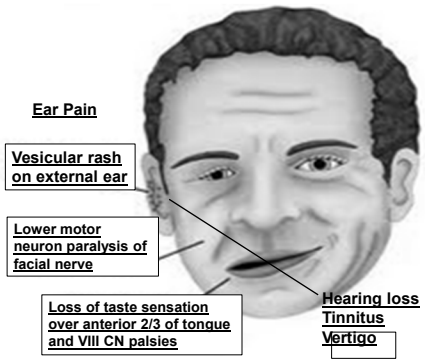


Fugate JE, January 2020, Practical Neurology

14

Ramsay-Hunt Syndrome: Herpes Zoster Oticus

Geniculate Ganglion of Cranial Nerve VII
External Ear Vesicles and Facial Nerve Paralysis



15

Prevention of Zoster

- Recombinant VZV glycoprotein E /adjuvant AS01B (RZV-Shingrix)
- Recommended in adults with HIV aged ≥18 years, regardless of CD4 cell count
- 2-dose series at 0 and then at 2 to 6 months
- RZV should not be given during an acute episode of herpes zoster

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

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Herpes Simplex

- Orolabial herpes: most common manifestation of HSV-1 infection
- Genital herpes: typically caused by HSV-2 but increasingly due to HSV-1 (recurrences and viral shedding less often with genital HSV-1)
- Proctitis in men who have sex with men; may not have external anal ulcers
- Dissemination: rare, even in severely immunosuppressed patients
- Other manifestations in PWH who have low CD4 counts (<100)
  - Esophagitis
  - Retinitis (acute retinal necrosis)
  - Chronic, extensive, deep genital ulcers, often acyclovir resistant

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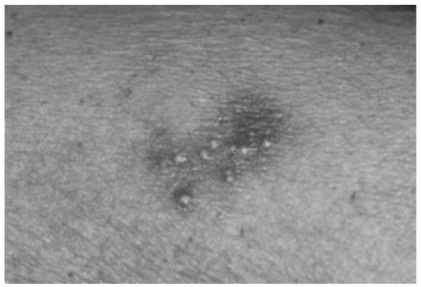
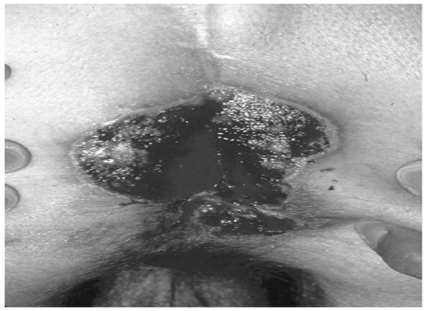
Localized Herpes Simplex



18

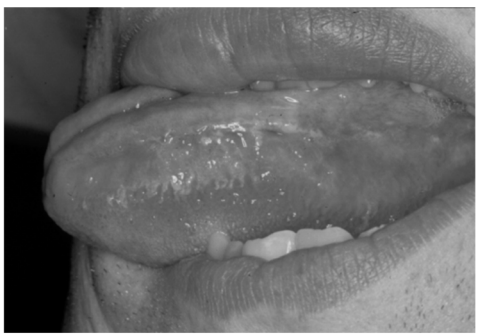
Chronic Extensive Perirectal HSV in PWH with Low CD4 Count

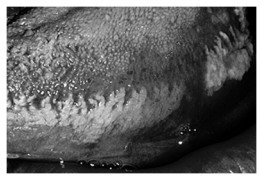


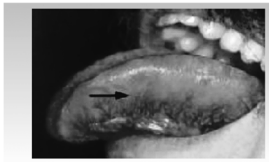
- Look for Acyclovir Resistance with Viral Culture and Phenotypic Testing
- Treatment for acyclovir-resistant HSV: iv foscarnet

19

Oral Hairy Leukoplakia EBV Associated

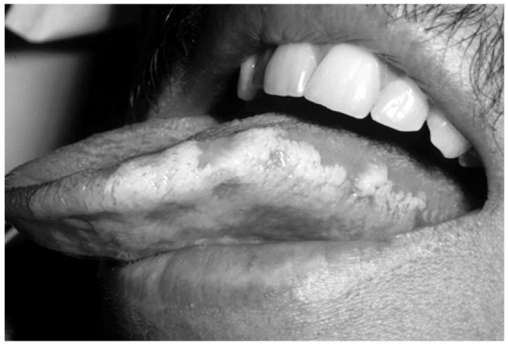






20

Oral Hairy Leukoplakia



Photograph from Mark Nichols, DDS, Dental Director, South Central AETC
https://www.hiv.uw.edu/go/basic-primary-care/oral-manifestations/core-concept/all

21

HIV Diseases Associated with EBV

- Oral Hairy Leukoplakia
- Primary CNS Lymphoma

22

Dermatologic Findings in PWH

Prurigo nodularis

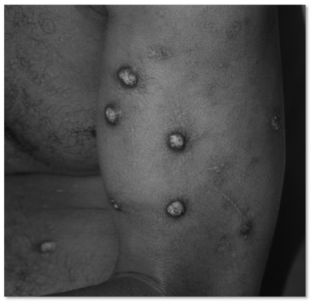
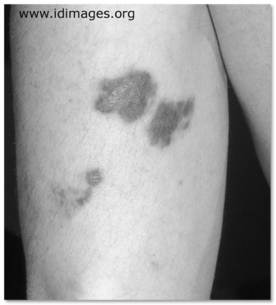


Image courtesy of Dr. Anisa Mosam

Kaposi Sarcoma (HHV-8 associated)



www.idimages.org

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HIV Associated Opportunistic Conditions: Part 3

Fungal Infections
(other than Cryptococcal Meningitis and Candida)

24

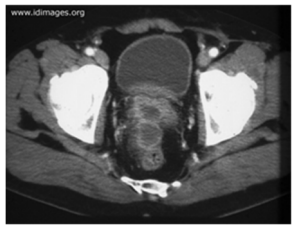
Fungal Diseases (other than Cryptococcal Meningitis and Candida) in Persons Living with HIV

- Cryptococcus: cutaneous, prostate
- Talaromyces
- Histoplasmosis
- Coccidioidomycosis

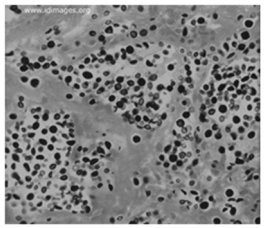
25

Cryptococcal Prostate Abscess

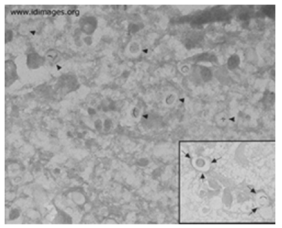
- Man with advanced HIV, CD4 cell count 40, HIV RNA 225,000 (not on ART) presented with 4 weeks of pain on defecation



Pelvic CT scan: Prostate Abscess



Silver stain of prostatic aspirate.

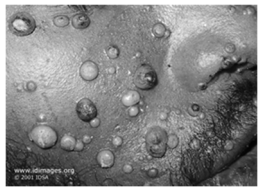


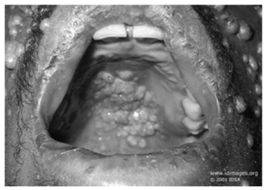
Hematoxylin and eosin stain.
www.idimages.org

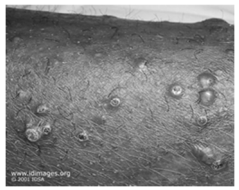
26

Mucocutaneous Cryptococcus

Man with advanced HIV, CD4 count <20 (not on ART) presented with fever, cough and skin lesions





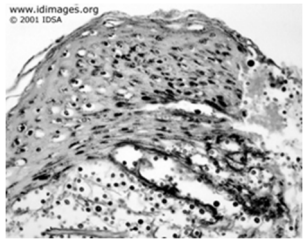


www.idimages.org

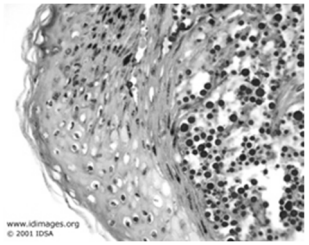
27

Mucocutaneous Cryptococcus

Man with advanced HIV, CD4 count <20 (not on ART) presented with fever, cough and skin lesions



Silver stain of skin biopsy



Mucicarmine stain of biopsy.

www.idimages.org

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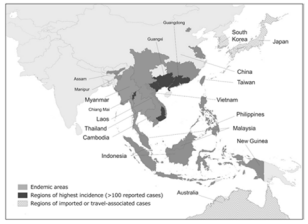
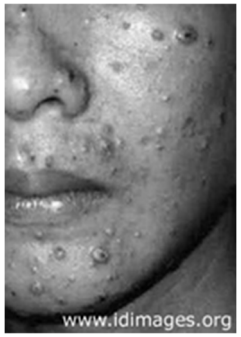
Talaromyces marneffei (formerly *Penicillium marneffei*)

- Dimorphic fungus endemic in SE Asia, East Asia, South Asia
- Advanced HIV is risk factor for severe disease
- Skin lesions: central-necrotic or umbilicated papules
- Pulmonary, GI involvement; hepatosplenomegaly

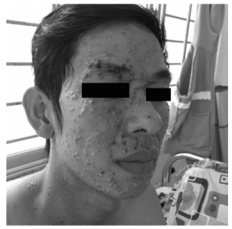


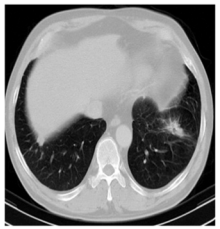


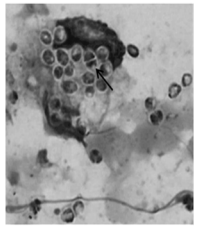
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/talaromycosis?view=full

29

Talaromyces marneffei (formerly *Penicillium marneffei*)







Round-to-oval organisms,
3 to 6 µm in diameter.
Midline septum in a dividing yeast cell

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

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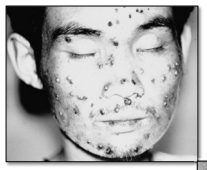
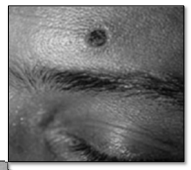
Skin Lesions for HIV Associated Endemic Mycoses May Be Difficult to Distinguish

Talaromyces

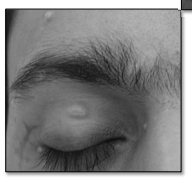


Histoplasmosis



Cryptococcosis

Molluscum

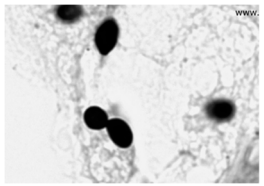


31

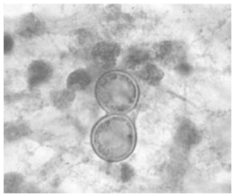
Other Fungal Diseases that are Covered Elsewhere in IDBR

- Look for questions on patients with HIV and….

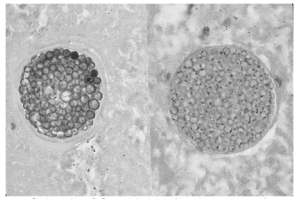
www.idimages.org



Narrow-based budding of *Histoplasma* (2-5 microns)



Broad based budding of *Blastomyces*
10-15 microns



Spherule of *Coccidioides* (25-100 microns)

"Pilot wheel" of *Paracoccidioides*
(10-20 microns)

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HIV Associated Opportunistic Conditions: Part 3

GI Complications

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Causes of Diarrhea in PWH

- **CMV Colitis**: bloody diarrhea, intestinal perforation in PWH with CD4 <100
- **Bacterial causes:** Salmonella, Shigella, Campylobacter, Enteroaggregative E coli; Clostridioides difficile; STIs/proctitis (LGV, GC, Syphilis); MAC (CD4 count <50: fevers, systemic symptoms)
- **Parasitic causes:** Microsporidia and Cryptospordia (CD4<100: chronic diarrhea, extra-intestinal manifestations); Cystoisospora (formerly Isospora); Cyclospora; Giardia; Amebiasis
- **Cancer:** Kaposi sarcoma, lymphoma
- **Medications:** antiretroviral therapy (particularly protease inhibitors), antibiotics

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

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Evaluating Diarrhea in PWH

- Acute diarrhea: stool C and S, C difficile testing
- Chronic diarrhea: above plus stool O and P, cryptosporidia, microsporidia, isospora, cyclospora stains; giardia antigen; if proctitis, STI testing
- Diarrhea, fever, systemic symptoms in PWH and low CD4 cell count: AFB blood cultures, CMV DNA
- Endoscopy: if evaluation above is unrevealing

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Salmonella in PWH

- Bacteremia more common in PWH (especially those with low CD4 count) than people without HIV
- Bacteremia merits HIV testing
- Recurrence common unless effective ART given

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Shigella

Update – CDC Recommendations for Managing and Reporting *Shigella* Infections with Possible Reduced Susceptibility to Ciprofloxacin

HAN HEALTH ALERT NETWORK
Distributed via the CDC Health Alert Network
June 7, 2018, 1100 ET (11:00 AM ET)

This is an official CDC HEALTH UPDATE

June 7, 2018

- Increasing number of Shigella isolates that test susceptible to ciprofloxacin (MIC 0.12 to 1 mcg/mL) but harbor resistance genes
- DHHS: consider treatment; may be withheld in PWH and CD4 >500 with mild symptoms or whose diarrhea is resolving before cultures return
- Counsel patients to wait to have sex for 1-2 weeks after diarrhea resolves

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

Slide 37

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Increase in Extensively Drug-Resistant Shigellosis in the United States

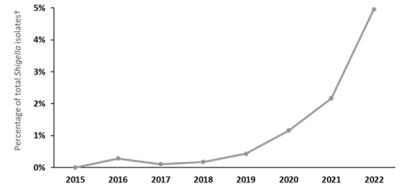
Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Feb 24, 2023

- ≃ 5% of Shigella now XDR: resistant to azithromycin, ampicillin, ciprofloxacin, ceftriaxone, TMP/SMX
- Men who have sex with men, people experiencing homelessness, international travelers, people with HIV



- No current treatment recommendations
  - In UK, oral Pivmecillinam and Fosfomycin or IV carbapenem and colistin (hospitalized)

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HIV Associated Opportunistic Conditions: Part 3

CMV

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CMV in PWH: Highlights

- Cause of end-organ disease in PWH who have CD4 count <50 and are not receiving ART
- End-organ disease:
  - Retinitis
  - Colitis
  - Esophagitis: odynophagia, retrosternal or mid-epigastric pain
  - Neurologic disease
  - Pneumonitis: rare in people with HIV; when CMV found in bronchoalveolar lavage, frequently a bystander

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

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Prevention of CMV Disease in PWH

- Antiretroviral therapy to maintain CD4 count >100
- Valganciclovir prophylaxis is NOT recommended

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

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Diagnosis of HIV Related CMV Disease

- **Serology**
  - Disease unlikely if IgG seronegative
- **Cytology**
  - Rarely useful
- **Biopsy**
  - Helpful if many inclusions and substantial inflammation
- **PCR**
  - Correlates with low CD4 Count
  - "Less than ideal" sensitivity and specificity for clinical disease

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

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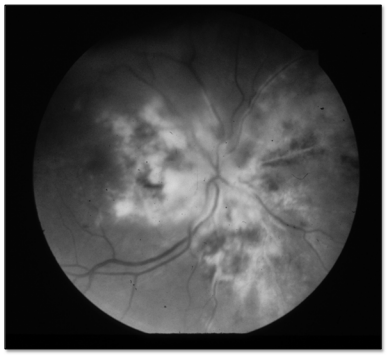
CMV Retinitis

- **Visual changes, decreased visual acuity**
- **Funduscopic exam**
  - Bilateral disease in 1/3
  - Mustard and Ketchup
  - Necrosis of retina
  - Little vitreal inflammation
- **PCR of blood not useful: 70% sensitive, but non-specific**
- **Vitreal taps for diagnosis with PCR rarely necessary**
  - Tap positive in 80% of cases



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

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Therapy for CMV Retinitis

- **Immediate sight-threatening lesions**
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (twice daily x 14–21 days), then daily for at least 3-6 months plus
  - Intravitreal ganciclovir weekly over several weeks until lesion inactivity
  - Ganciclovir implant no longer manufactured
- **Small peripheral lesions**
  - ART
  - Oral valganciclovir for at least 3-6 months and immune reconstitution
  - +/- intravitreal ganciclovir

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

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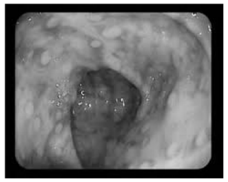
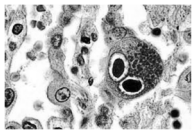
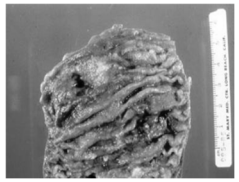
CMV Colitis

- **Clinical Presentation**
  - Fever, anorexia, abdominal pain, diarrhea
  - May cause perforation, hemorrhage
  - CT may show colonic thickening or mass
- **Diagnosis**
  - Colonoscopy with cytology or biopsy: mucosal ulcerations, intranuclear and intracytoplasmic inclusions, immunohistochemistry
  - PCR non-specific
- **Therapy:** Ganciclovir, Valganciclovir. Alternative: Foscarnet

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

45

CMV Colitis

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CMV Neurologic Disease

- **Encephalitis**
- **Ventriculoencephalitis**
  - Focal neurologic signs, rapid progression
  - Peri-ventricular enhancement on MRI or CT imaging
- **Polyradiculomyelopathy or transverse myelitis**
  - Radicular back pain, urinary retention, bilateral leg weakness
  - Spastic myelopathy, sacral paresthesia
  - CSF: neutrophilic pleocytosis (100-200), low glucose, elevated protein

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

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Thank you

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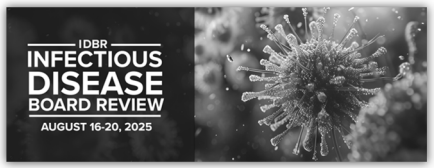
Online Only Lectures

OL7

Even More Worms

Edward Mitre, MD

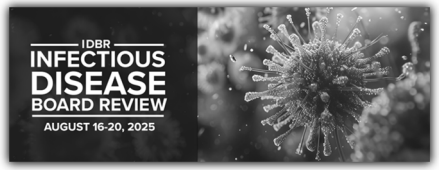


Even More Worms!

Edward Mitre, MD
Rockville, MD

Disclaimer: Dr. Mitre is giving this presentation in a personal capacity. The views expressed in this presentation are the sole responsibility of the presenter and do not necessarily reflect the views, opinions, or policies of the Uniformed Services University of the Health Sciences, the Department of Defense, or the United States Government.

1



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

2

Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Dibothriocephalus latus*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

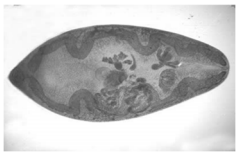
Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *(Dracunculus medinensis)*

3

Trematodes (Flukes)

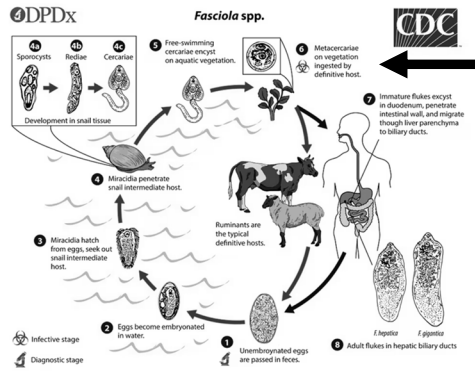
- Flat, fleshy, leaf-shaped worms
- Usually have two muscular suckers
- Usually hermaphroditic (except Schistosomes)
- Require intermediate hosts (usually snails or clams)
- Praziquantel treats all (except *Fasciola hepatica*)



Paragonimus (CDC DpDx)

4

Fasciola hepatica (“Sheep Liver Fluke”)



Cercariae have to encyst on vegetation!

F. hepatica (2-3 cm in length)
Worldwide distribution in tropical areas (high prevalence: Bolivia, Peru)

F. gigantica (up to 7.5 cm in length)
Present in Africa, SE Asia, Pacific

5

Fasciola hepatica (“Sheep Liver Fluke”)

- Acquired by eating encysted larvae on aquatic vegetation (e.g., Water chestnuts)
- Fluke migration through the liver: RUQ pain and hepatitis
- Arrive at biliary ducts in liver and mature over 3-4 months
- Can induce biliary obstruction

F. hepatica
(CDC DpDx)

Dx: eggs in stool exam (low sensitivity), serology

Rx: triclabendazole (FDA approved in 2019!)

(***Note: fasciola species are the only trematode parasites of humans that don’t respond well to praziquantel)

6

Clonorchis sinensis

“Chinese Liver Fluke”

China, Japan, Eastern Russia, Korea, Vietnam

- Eggs →snails →freshwater fish
- Acquisition by ingestion of undercooked fish
- Flukes develop in duodenum then migrate to liver bile ducts
- Can live for > 15 years, making 2000 eggs/day
- Cats and dogs can serve as reservoirs

Opisthorchis viverrini

“Southeast Asian Liver Fluke”

- Similar lifecycle
- Also acquired by eating fish

Both can cause:

- **Biliary obstruction**
- **Cholelithiasis**
- **Cholangiocarcinoma**

7

Paragonimus westermani “Lung Fluke”

Eggs→snails→freshwater crabs and crayfish

Ingestion of undercooked seafood

(China, Japan, Korea, India, Philippines)

Adults migrate to LUNGS, frequent EOSINOPHILIA

Symptoms:

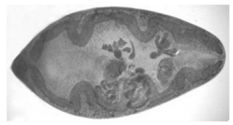
- *Fever, cough, diarrhea during acute migration*
- *Later, may have chest pain as worms migrate through lungs*
- *Can develop chronic pulmonary symptoms*

Dx: Sputum and/or stool exam for eggs, serology

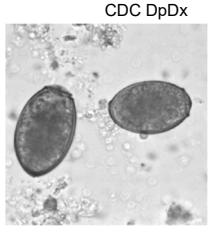
NOTE: Cases of Paragonimus kellicotti acquired in U.S. by ingestion of raw crayfish in rivers in Missouri!

CID 2009 Sep 15;49(6):e55-61.

Clin Microbiol Rev 2013 Jul;26(3):493-504



CDC DpDx



CDC DpDx

8

Intestinal Flukes

Fasciolopsis buski
("Giant Intestinal Fluke" 2 cm w x 8 cm)
- Acquisition: eating encysted larval stage on aquatic vegetation
- Symptoms: usually asymptomatic
  - Can cause diarrhea, fever, abdominal pains, ulceration, and hemorrhage

Dx: eggs in stool

Metagonimus yokagawi
(2.5mm x 0.75mm)
- Acquisition: eating larvae in undercooked fish
- Symptoms: diarrhea and abdominal pain

9

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- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Dibothriocephalus latus*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

NEMATODES

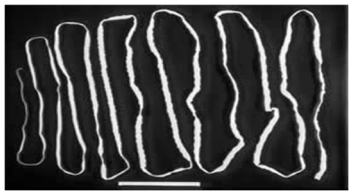
Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

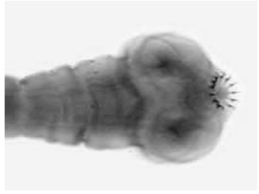
Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *(Dracunculus medinensis)*

10

Cestodes (Tapeworms)

- All (except *D. latum)* have suckers with surrounding hooklets on the scolex (head) to attach to intestinal lining
- Have flat, ribbon-like bodies composed of proglottid segments which contain reproductive organs
- Have no digestive systems (food absorbed through soft body wall of worm)

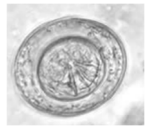




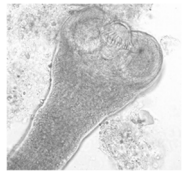
11

Hymenolepis nana

"Dwarf tapeworm" (4-6 cm long)
Found worldwide → the most common cestode infection of humans
Predator (larval stage): rodents, humans
Prey (tapeworm stage): beetles!
Acquisition: by ingestion of eggs in contaminated food or water
OR by ingestion of infected grain beetle!
Symptoms: Often asymptomatic
With large parasite burdens, can cause
-loose stools, diarrhea
-crampy abdominal pain
-weakness
Diagnosis: finding eggs or proglottid segments in stool
(note: sometimes confused for pinworms)
Treatment: praziquantel 25 mg/kg x 1, repeat dose in 10 days
(higher than for most tapeworm infections)



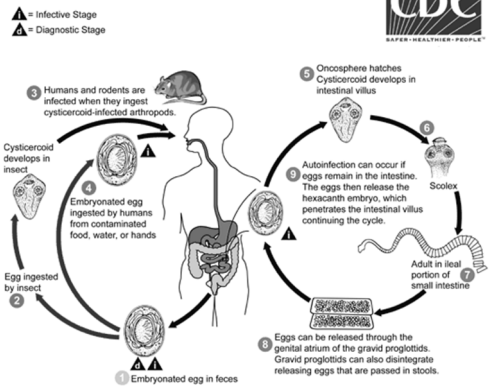
H. nana egg in wet mount
(note the hooklets)
CDC DpDx



H. nana scolex in stool sample
(note the hooklets and suckers)
CDC DpDx

12

Hymenolepis nana



13

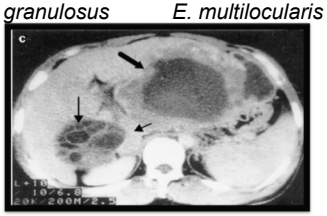
Echinococcus multilocularis

Fox/rodent lifecycle

Causes an infiltrative, tumor-like growth in liver

- → poorly demarcated
- → has a semi-solid nature (does <u>not</u> form large cysts)

E. granulosus *E. multilocularis*



Lancet 2003,362:1295-304

14

Major Helminth Pathogens

<u>TREMATODES</u>

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

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- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *(Dracunculus medinensis)*

15

Nematodes (Roundworms)

- Non-segmented round worms
- Flexible outer coating (cuticle)
- Muscular layer under the cuticle
- Nervous, digestive, secretory, and reproductive systems

16

How Do People Get Infected with Nematodes?

1. Eating eggs in fecally contaminated food or soil
   Ascaris, Trichuris, Enterobius, and Toxocara
2. Direct penetration of larvae through skin
   Hookworms, Strongyloides
3. Eating food containing infectious larvae
   Trichinella, Angiostrongylus, Anisakis
4. Vector transmission
   Wuchereria, Brugia, Oncho, Loa

17

Paracapillaria philippinensis

Epidemiology: primarily SE Asia

Risk factor: **eating raw freshwater fish**

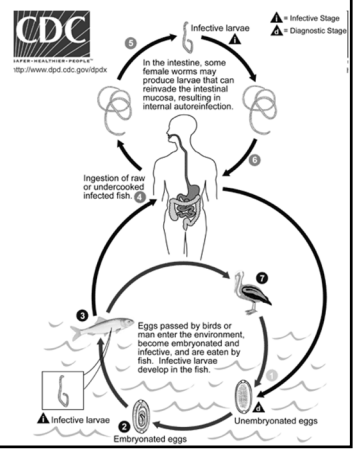
Sxs:

Often initially asymptomatic

Over time develop:

- borborygmus
- abdominal pain
- watery diarrhea

→ If not treated over weeks to months get large electrolyte losses and dehydration which can lead to death



18

Paracapillaria philippinensis

Pathogenesis:

Eat infected raw fish

→ larvae released into intestine

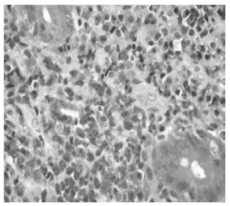
→ grow to adults which burrow in mucosa

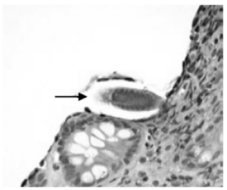
→ female worms lay eggs (oviparous)

→ some female worms are larviparous

→ some larvae burrow into the intestinal lining and develop into adults

→ over weeks to months the worm burden increases (from a few worms to tens of thousands) and symptoms progress

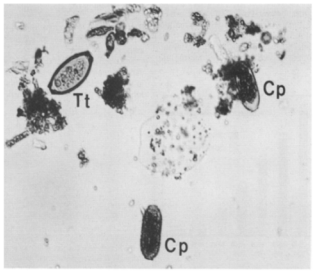




N Engl J Med 2008;359:75-80.

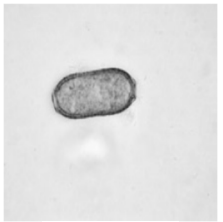
19

Paracapillaria philippinensis



1. Eggs of *C. philippinensis* (Cp) compared with an egg of *T. trichiura* (Tt). Magnification, ×160.

Cross J, Clin Micr Reviews, 1992



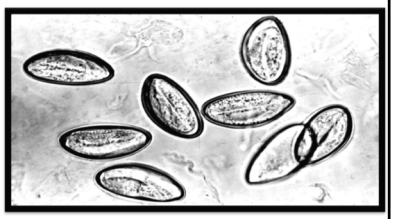
N Engl J Med 2008;359:75-80.

Dx: stool o/p (eggs similar to Trichuris)

Rx: 10 d course albendazole + supportive Rx (IVF, replete electrolytes, etc.)

20

Enterobius vermicularis
(Pinworm)



- Found everywhere
- Fecal/oral
- Humans are the only hosts
- Peri-anal itching
- Also: vaginal itching/discharge (vulvovaginitis) nausea/abdominal pain, rare: appendicitis

Dx: stool o&p exams not very helpful
- → "pinworm paddle test" early am before showering or defecating, multiple tests increase sensitivity
- → eggs have one flat side

Rx: pyrantel pamoate, albendazole, or mebendazole single dose
- → **treat all members of household**
- → **retreat everyone in two weeks**
- → careful trimming of fingernails, hand washing, washing of bedclothes to rid house of eggs

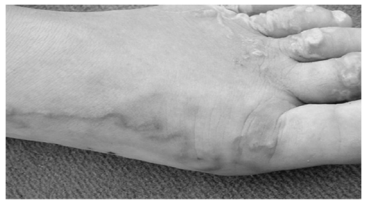
21

Question #1

A 13-year-old girl developed a pruritic rash on her foot after moving to rural northeast Florida.

Which of the following helminths is the most likely cause of the rash?

A. *Enterobius vermicularis*
B. *Ascaris lumbricoides*
C. *Trichuris trichiura*
D. *Toxocara canis*
E. *Anyclostoma caninum*



Am Fam Physician 2010, 81(2): 203-4.

22

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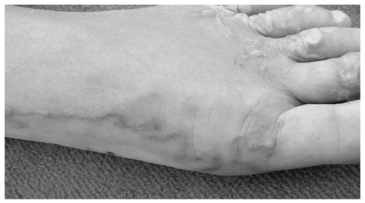

Am Fam Physician 2010, 81(2): 203-4.

23

Cutaneous Larva Migrans

Creeping eruption caused by dog or cat hookworms

Ancylostoma caninum
Ancylostoma braziliense
Uncinaria stenocephala

- Worms migrate laterally
- Unable to penetrate basal membrane of human skin
- Can occur 2-8 weeks after exposure

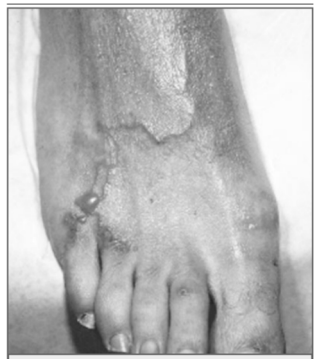

Figure 1. **Cutaneous Larva Migrans Caused by *Ancylostoma braziliense*.**

N ENGL J MED 351;8 WWW.NEJM.ORG AUGUST 19, 2004

24

Major Helminth Pathogens

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- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *(Dracunculus medinensis)*

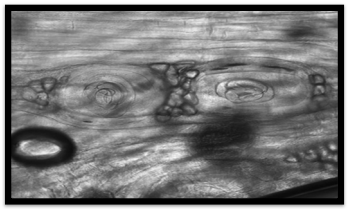
25

Trichinellosis

(T. spiralis and, in Africa, T. nelsoni)

1. Eat meat containing cysts. (pork, boar, horse, wild game)
2. Larvae are released from cysts by gastric acid
3. Adults invade sm. Bowel, and mature into adults over 1-2wks*
   --> ABDOMINAL CRAMPS,
   DIARRHEA IF HEAVY INFXN
4. Adults (who only live for about a month) produce larvae.
5. Larvae migrate to striated muscle, encyst, and live in "nurse cells
   - **MUSCLE PAIN**
   - **PERIORBITAL EDEMA**
   - **EOSINOPHILIA**
   - OCC CNS AND HEART DAMAGE
     +/- Fever and Urticaria

*Molt four times within 40h and then copulate within hours after final ecdysis. Newborn larvae (NBL, L1 larvae) can be released as soon as 4 days after infection! (4 larval stages, 1 adult stage) PMID: 11895947



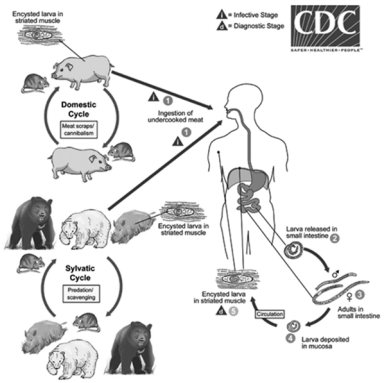
CDC DPDx

Diagnosis:
- Serologies are supportive
- + Biopsy is definitive

Treatment:
- Albendazole + steroids

26

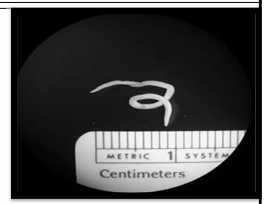
Trichinellosis



27

Anisakis

Larvae are typically 1.5-3.0 cm in length



CDC DPDx

Ingestion of larvae in raw or undercooked seafood (found worldwide)
In humans, parasite buries its head into gastric mucosa. Eosinophilia common.

Symptoms
- Due to invasion of worm (pain, vomiting)
- Due to allergic rxn to worm
  (mild urticaria, itchy sensation back of throat, anaphylactic shock)

Treatment

→ usually simple endoscopic removal
→ for allergic symptoms, avoid contaminated fish

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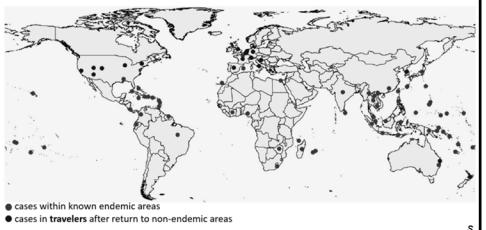
Angiostrongylus

The most common parasitic cause of eosinophilic meningitis worldwide

Appears to be spreading in range

Acquisition by eating raw or undercooked
- Snails or slugs
- Freshwater prawns, shrimps, crabs, frogs
- Contaminated produce (leafy greens)

A. cantonensis



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2022, Am. J. Trop. Med. Hyg, 107 (6):1166-72
Creative Commons License

Two species cause disease in humans

A. cantonensis – **eosinophilic meningoencephalitis**

→ China, SE Asia, Japan, Australia, Pacific basin, Hawaii, Caribbean, Africa, everywhere

A. costaricensis – **inflammation of the GI tract (abdominal angiostrongyliasis)**

maturation of larvae in intestinal wall

eosinophilic granulomas on histopathology of intestinal biopsies

→ Central and South America

29

Angiostrongylus in Florida!

Snails and rodents in Florida have been documented to harbor Angiostrongylus for several years

Between June 2021 and Jan 2022

→ Three pediatric cases of eosinophilic meningitis due to Angiostrongylus were reported in Florida

19-month-oldresented with refusal to walk
- Geophagia sand at beach
- 21-day hospitalization

10-year-old presented with 3 weeks of progressive headache and vomiting
- Had eaten a snail 1 month prior on a dare
- Prolonged hospitalization with intubation

8-month-old presented with fever, vomiting, lethargy, and left-sided esotropia
- No h/o unusual ingestions
- 14-day hospitalization

In all three cases Angiostrongylus was identified by cell-free DNA next-gen sequencing (Karius®) of plasma

Journal of the Pediatric Infectious Diseases Society, Volume 13, Issue 12, December 2024, Pages 639–642, https://doi.org/10.1093/jpids/piae113

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Angiostrongylus cantonensis

Prevention (recommendations from the Hawaii DOH)

→ Do not eat raw/undercooked snails or slugs, freshwater prawns, shrimps, crabs, frogs

→ Inspect and rinse all produce, especially leafy greens

→ Wear gloves when handling snails or slugs and wash hands after handling snails or slugs

Also: rodent eradication and freezing of mollusks and crustaceans

https://health.hawaii.gov/docd/disease_listing/rat-lungworm-angiostrongyliasis/#info_for_clinicians

Diagnosis
- Usually presumptive
  (eosinophilic meningitis + exposure history)
- Serology (not commercially available)
- CSF PCR (Hawaii DOH State Laboratory, NIH as research assay)

Treatment: corticosteroids + albendazole

(see 2021 Guidelines paper in Parasitology, 148,227-233. PMID:32729438)

31

Question #2

A 6-year-old boy from Indiana who has a pet dog and likes to play in a sandbox presents with fever, hepatosplenomegaly, wheezing, and eosinophilia. He has never travelled outside the continental U.S.

What is the most likely causative agent acquired in the sandbox?

A. *Anisakis simplex*
B. *Onchocerca volvulus*
C. *Enterobius vermicularis*
D. *Toxocara canis*
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32

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D. ***Toxocara canis***
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33

Toxocariasis (and Baylisascariasis)

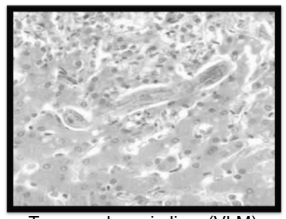
Due to dog (*Toxocara canis*), cat (*Toxocara cati*), and raccoon (*Baylisascaris procyonis*) ascarids.

Humans acquire infection by ingestion of animal feces.
In humans → larvae hatch in intestine and migrate to liver, spleen, lungs, brain, and/or eye.

Symptoms

Visceral Larva Migrans (VLM)
usually 2-5 year olds
fever, eosinophilia, hepatomegaly
also wheezing, pneumonia, splenomegaly

Ocular Larva Migrans (OLM)
often in 10-15 year olds
retinal lesions that appear as solid tumors


Toxocara larva in liver (VLM)

Baylisascaris often more severe and more likely to cause CNS disease (eosinophilic meningitis)

CDC DPDx

34

Toxocariasis

Dx: clinical picture + Toxocara antibody testing
(serum and intraocular fluid by ELISA testing)

NOTE: Toxocara IgG is only supportive b/c many individuals have + Ab due to prior exposure

Rx: usually self-limited disease
acute VLM or OLM can be Rx with albendazole and steroids

35

Gnathostoma spinigerum and hispidum

Undercooked freshwater fish (ceviche!), frogs, birds, reptiles
Asia (esp. Thailand), Central/South America, parts of Africa

→ Disease due to migrating immature worms
→ Often with peripheral eosinophilia
→ May have initial epigastric pain, nausea, vomiting as worms penetrate GI tract and migrate to tissues

SKIN: migratory, painful subcutaneous swellings (recur every few weeks, can last for years)
creeping eruption/cutaneous larva migrans

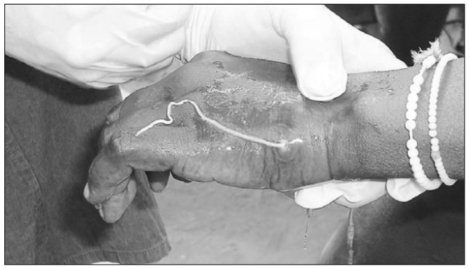
TISSUE: visceral larva migrans
eosinophilic meningoencephalitis
radiculomyelitis
ocular disease (anterior and posterior uveitis)

Dx: empiric or by biopsy, no antibody test available in the U.S.

Rx: can be difficult, may require 3 weeks of albendazole

36

What is this?

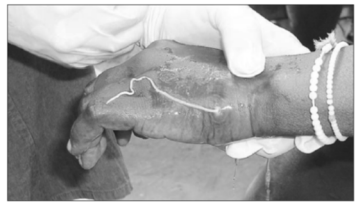


Emerging Guinea Worm.

37

Dracunculus medinensis

(fiery serpent, affliction with little dragon)



Emerging Guinea Worm.

N ENGL J MED 356;25 WWW.NEJM.ORG JUNE 21, 2007

- Acquired by drinking water contaminated with microscopic copepods ("water fleas")
- One year after a person is infected, adult female worms emerge and expel their larvae
- Adult worms can be >2 feet long.
- Worm emergence is excruciatingly painful
  - → predisposes to bacterial superinfection
  - → can lead to disability for months
- No effective medical therapy → treatment is slow manual extraction
- Global eradication campaign since 1980s, down to less than 10 cases per year
- Infection is preventable by
  - → filtering water through fine cloth to remove copepods
  - → not walking in drinking water
  - → killing copepods and larvae with chemicals applied to drinking water
- Complete eradiation has been elusive as some animals, especially dogs, can serve as reservoirs

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Caveat to today's talk – a bit simplistic
Multiple parasites can cause similar diseases

Eosinophilic meningitis

Nematodes
- **Angiostrongylus cantonensis (rat lung worm)**
- **Baylisascaris procyonis (racoon ascarid)**
- **Gnathostoma species**
- Toxocara canis & T. cati
- Trichinella spiralis
- Strongyloides stercoralis
- Loa loa
- Meningonema peruzzi (filaria of monkeys)

Trematodes
- Schistosoma species (larvae or eggs)
- Paragonimus westermani
- Fascioliasis

Cestodes
- Neurocysticercosis
- Echinococcus

Non-helminth infections
- Fungi (esp. Coccidiodes and Cryptococcus
- Myiasis with CNS entry
- Bacteria (very rare; Tb, syphilis, Rickettsia, Strep)
- Viruses (very rare; LCMV, Coxsackie)
- Protozoa (very rare; Toxoplasmosis)

Malignancies
- Hodgkin's
- NHL
- AML
- Meningeal carcinomatosis
- Glioblastoma

Primary Hypereosinophilic Syndromes

Inflammatory/allergic reacitons
Medications (NSAIDS, ciprofloxacin, contrast dye)
VP shunt, other foreign bodies

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Good Luck!

Ed Mitre
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Online Only Lectures

OL8

Statistics

Khalil Ghanem, MD

Epidemiology for the Boards

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1

Disclosures

- None

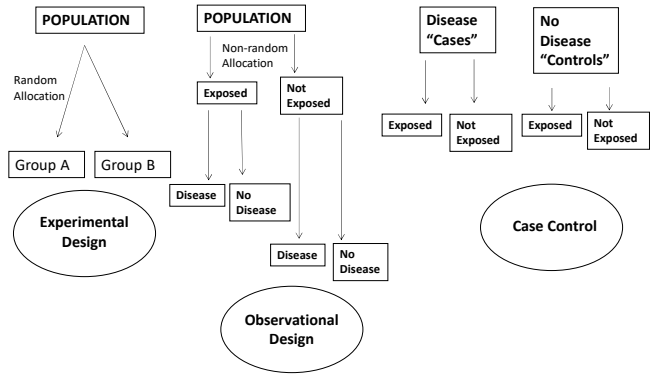
2

Overview

- Study designs
- Incidence & Prevalence
- Relative risk, relative odd, & attributable risk
- Confidence intervals
- Number needed to treat
- Sensitivity, specificity, positive predictive value, negative predictive value
- Bias and confounding

3

Study Designs



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Example: Study Designs

- **Choose the most appropriate study design for the following scenarios:**
  - You are trying to determine what caused 35 people to experience fever and severe hemorrhagic complications upon returning from a Caribbean cruise
  - You want to get FDA approval for a novel influenza vaccine
  - You want to determine whether hormonal contraception increases your risk of HIV

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Incidence vs. Prevalence

- **Incidence**= *new* infection occurring during a specified period of time in a population at risk for developing the infection
  - A measure of events (a disease that develops in someone who did not have it), thus, a measure of *risk*
- **Prevalence:** number of affected persons present in the population at a given time(i.e. *existing* infections)
- **Prevalence=Incidence X duration of disease**

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Example: Incidence vs. Prevalence

- **In a population that includes persons with HIV who exhibit high medication adherence, what would the impact of ART be on HIV incidence and prevalence over a 10 year period?**

  -Incidence= new HIV infections. ART should decrease the risk of transmission of HIV and thereby **decrease** the incidence

  -Prevalence= all existing HIV infections. ART allows people with HIV to live longer so it may **increase** the prevalence of HIV

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Estimating Risk

- **Relative Risk (RR)**= Incidence in exposed/ Incidence in nonexposed
  - If the RR=1, there is no association
  - If the RR >1, the risk in exposed > nonexposed
  - If the RR<1, the risk in exposed < nonexposed
- **Hazards Ratio(HR)**: A form of RR; HR is instantaneous while RR is cumulative.
- **Odds**= Probability that disease developed/Probability that it did not develop
- **Odds Ratio:**
  - **Cohort study:** ratio of odds of disease occurring in exposed to the odds of disease occurring in non-exposed
  - **Case Control**: ratio of the odds that the cases were exposed to the odds that the controls were exposed
  - If the OR=1, there is no association between exposure and disease
  - If the OR>1, the exposure is positively related to the disease
  - If the OR<1, the exposure is negatively related to the disease

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Example: Estimating Risk

- **In a population of 1000 people, 400 were having condomless sex. Infection-Y occurred in 100 of the 400 who were having condomless sex and in 5 of the 600 who were not.**
- **What is the RR of Y in those having condomless sex?**
- **What are the relative odds (odds ratio) of Y in those having condomless sex?**

- RR: 100/400/5/600= 31.3
- OR: 100/300/5/595=41.3

- The odds ratio is a good estimate of the relative risk when the disease being studied is RARE

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Estimating Risk 2

- The **attributable risk** is the proportion of disease incidence that can be attributed to a specific exposure

  AR= Incidence in exposed- Incidence in non-exposed
- This is one of the most important measures when deciding *how* to spend money and resources in public health

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Example: Estimating Risk 2

A new deadly fungal infection is described with a mortality rate of 30%.

You are given 1 million dollars to spend on prevention in your state.

-Persons with Exposure A have a RR of 16 for getting infected.

-Persons with Exposure B have a RR of 2 for getting infected.

How will you spend your money?

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Example: Estimating Risk 2

- Exposure A is spelunking and Exposure B is gardening
  - **NOW how are you going to spend your money?**
- Even though the relative risk of spelunking is far more than gardening, most of the cases in your state are likely the result of gardening (a lot more people garden).
- The attributable risk of gardening, therefore, is much greater than that of spelunking

Exposure	Incidence	Relative Risk	Attributable Risk
Spelunking	32 per million	**16**	30 per million
No Spelunking	2 per million		
Gardening	640 per million	2	**320 per million**
No Gardening	320 per million		

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Confidence Intervals

- Confidence intervals (CI) are used to indicate the reliability of an estimate
  - CI is *directly* related to the standard deviation and *indirectly* related to the sample size (i.e. the larger the sample size, the smaller the CI)
- In simple terms, a 95% CI means: If you were to repeat this experiment many times, 95% of the time, your results will fall within this range.
  - The wider the CI surrounding the point estimate, the more uncertainty there is about the reliability of that point estimate

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Example: Confidence Intervals

- Match each scenario to the more likely prevalence point estimate and CI:
  - **Scenario 1**: We test 100 people in the population for HIV.
  - **Scenario 2**: We test 3500 people in the population for HIV

A. The prevalence of HIV is 1.3% (95%CI: 1.1 %-1.5%)
B. The prevalence of HIV is 3.3% (95%CI: 0.3%-7.2%)

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Number Needed to Treat (NNT)

- NNT= 1/(Rate in untreated)- (Rate in treated)

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Example: NNT

RCT for a new Ebola vaccine: the mortality rate in the experimental group is 20 per 100 while the mortality rate in the control group is 85 per 100. How many people do we need to vaccinate to prevent one death from Ebola?

NNT= 1/(0.85-0.20)=1.5

1.5 people need to be vaccinated to prevent a single death from Ebola. This would be a GREAT public health intervention in endemic areas.

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Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)

	Disease	No Disease
Positive	True Positive	False positive
Negative	False negative	True negative

Sensitivity= TP/ TP + FN
Specificity= TN/ TN +FP
PPV= TP/ TP + FP
NPV= TN/TN +FN

Sensitivity and specificity are INDEPENDENT of prevalence whereas PPV and NPV are DEPENDENT on prevalence

- **Sensitivity**= the ability of a test to correctly identify those who have a disease
- **Specificity**=the ability of a test to correctly identify those who do not have a disease
- **PPV**= the proportion who test positive and actually have the disease
- **NPV**=the proportion who test negative and actually don't have the disease

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Example: Sensitivity Specificity, PPV, NPV

The glycoprotein-G- based antibody tests for the detection of HSV-2 antibodies have a sensitivity of 99% and specificity of 98.5%. We plan to test two populations: (A) 1000 commercial sex workers (B) 1000 nuns confined to a convent.

In which population will the tests have a higher: Sensitivity? Specificity? PPV? NPV?

- Sensitivity and specificity are INDEPENDENT of prevalence of disease. As such, the sensitivity and specificity of these tests will be the same in both populations
- Population A likely has a higher prevalence of HSV-2 compared to population B. As such, the PPV of the test will be higher in population A and the NPV will be higher in population B

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Definitions

- **Precision**: How close do the results cluster to ***each other***?
- **Accuracy**: How close do the results cluster to ***the truth***?
- **Bias**: systematic error leading to a decrease in accuracy
  - Bias is reduced by careful study design
- **Confounding**: a distortion in the degree of association between an exposure and an outcome due to a mixing of effects between the exposure and an incidental factor, which is known as the confounder
  - **You must adjust for confounding; otherwise, it will lead to misinterpretation of results**
- **Effect Modification** (i.e. interaction): a variable that differentially (positively and negatively) modifies the observed effect of a risk factor on disease status. Different groups have different risk estimates when effect modification is present
  - **Effect modification is a true phenomenon that should be reported. You do NOT need to adjust for it.**

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Example: Definitions

- Drinking coffee is found to be strongly associated with an increased risk of HPV-induced cervical cancer. We later find out that those who drink coffee are much more likely to smoke cigarettes.
- Cigarette smoking is a _____ in the relationship between coffee drinking and cervical cancer

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Thank you!

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Online Only Lectures

OL9

Epididymitis, Orchitis, and Prostatitis

Barbara Trautner, MD

Prostatitis, Epididymitis, and Orchitis

Barbara Trautner, MD, PhD

Professor of Medicine
Baylor College of Medicine
Houston, Texas

7/23/2025

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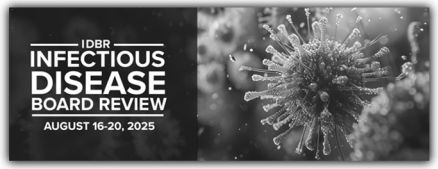


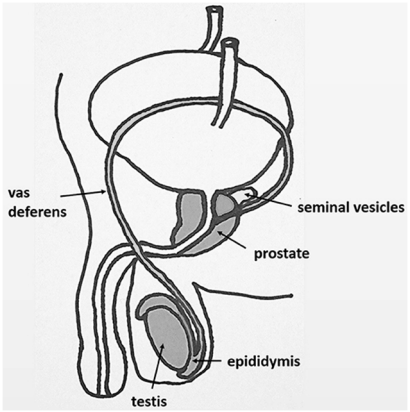
Disclosures of Financial Relationships with Relevant Commercial Interests

- **Current:** Shionogi (COVID trial)
- **Past:** Genentech, Pfizer, Abbvie, Abbott Laboratories, Bristol Myers Squibb, Phiogen, Peptilogics

2

Overview

- Epididymitis
- Prostatitis
  - Acute
  - Chronic
- Prostate biopsy
- Orchitis



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Case #1

A 72-year-old man presented to the emergency room with fever, urinary retention. No culture sent. Sent home with transurethral catheter and ciprofloxacin. Walked into Infectious Diseases clinic one month later with the urinary catheter is still in place. Temp 102.5, costovertebral angle tenderness present on exam. Admitted and started on ciprofloxacin.

Blood cultures: *Serratia marcescens (sensitive to cipro)*

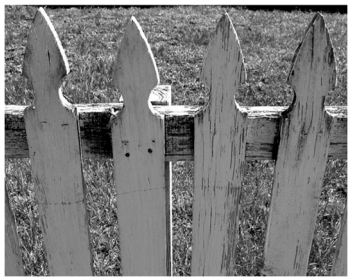
Urine cultures: *Serratia marcescens and Klebsiella pneumoniae (both sensitive to cipro)*

On hospital day 2, he is still febrile to 102.3, and he reports right testicular pain/swelling. He says this was present for the past 7 days but is more obvious now.

4

Question #1

Given his fevers on 2 days of ciprofloxacin, and the new awareness of right testicular pain and swelling, **what would be your next step?**



A. Add vancomycin to cover enterococci
B. Order a scrotal ultrasound
C. Add doxycycline for coverage of sexually transmitted infections
D. Consult urology emergently for testicular torsion

5

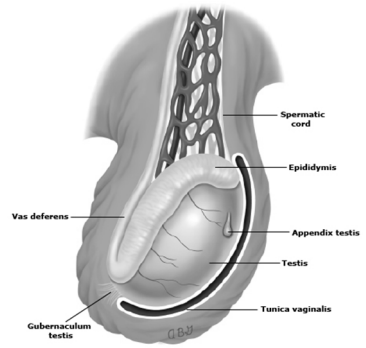
Question #1

Given his fevers on 2 days of ciprofloxacin, and the new awareness of right testicular pain and swelling, **what would be your next step?**

A. Add vancomycin to cover enterococci--no, we already know the causative organisms, and both are covered by ciprofloxacin
B. Order a scrotal ultrasound – yes, let's see what's going on with that right testicle
C. Add doxycycline for coverage of sexually transmitted infections – no, we already know he has bacteremia from a urinary source, and persistent fever at 48 hours is normal for pyelonephritis and epididymitis
D. Consult urology emergently for testicular torsion – this is not a leading concern, and if he had torsion for 48 hours, you are already too late

6

Normal testicular anatomy



The testicle is vertical and its anterior portion is surrounded by the tunica vaginalis.

7

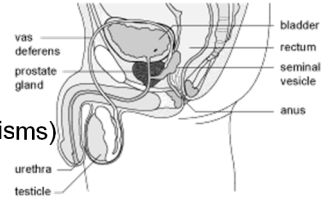
Epididymitis: Clinical Presentation

- Testicular pain, swelling, and tenderness
- Scrotal erythema
- Fever
- Dysuria or other urinary irritative symptoms
- Urethral discharge
- Reactive hydrocele can occur
- Epididymo-orchitis if testes also inflamed
- Gradual onset (if sudden, consider testicular torsion)
- Cremasteric reflex is preserved

8

Risk Factors for Epididymitis

- Urinary outlet obstruction
- Prostate biopsy
- Urinary tract instrumentation
- Immunosuppression (atypical organisms)
- Insertive anal intercourse
- Sexually transmitted infection
- Any condition that facilitates retrograde flow of urinary bacteria



Workowski et al, Sexually Transmitted Infections Treatment Guidelines, 2021
Recommendations and Reports / Vol. 70 / No. 4
UpToDate Acute Scrotal Pain in Adults

9

Etiologic Agents of Epididymitis

>14 and < 35 years of age: typically sexually transmitted

- *Neisseria gonorrheae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

Chronic or atypical

- *Mycobacterium tuberculosis*
- *Brucellosis*
- *Nocardia*
- *Blastomycosis*

> 35 years of age: enteric flora or spread from urine

- *Escherichia coli*
- *Klebsiella*
- *Proteus*
- *Pseudomonas*
- Enterococci

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

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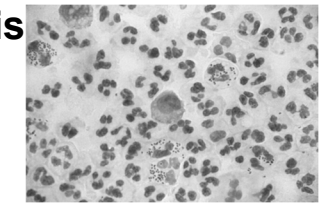
Workup of Epididymitis

- Physical exam
  - Intact cremasteric reflex
  - Testes in normal location
  - No draining sinus
- Gram stain of urethral secretions
- Urinalysis and urine culture
- Nucleic acid amplification test (NAAT) of urine
  - *N. gonorrhoeae*
  - *C. trachomatis*
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Scrotal ultrasound
- Call urology if concern for torsion



https://en.wikipedia.org/wiki/Neisseria_gonorrhoeae

Gram stain of urethral discharge

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Differentiating Epididymitis from Torsion

Table 1. Selected Differential Diagnosis of Acute Scrotum

Condition	*Typical presentation*	*Examination findings*	*Ultrasound findings*
Epididymitis	Gradual onset of pain that occasionally radiates to the lower abdomen; symptoms of lower urinary tract infection	Localized epididymal tenderness that progresses to testicular swelling and tenderness; normal cremasteric reflex; pain relief with testicular elevation (Prehn sign)	Enlarged, thickened epididymis with increased blood flow on color Doppler
Orchitis	Abrupt onset of testicular pain	Testicular swelling and tenderness; normal cremasteric reflex	Testicular masses or swollen testicles with hypoechoic and hypervascular areas
Testicular torsion	Acute onset of pain, usually severe	High-riding transversely oriented testis; abnormal cremasteric reflex; pain with testicular elevation	Normal-appearing testis with decreased blood flow on color Doppler

Trojian, American Family Physician, 2009

12

Treatment of Epididymitis

- If patient is low risk for sexually transmitted infection
  - Examples: recent urologic procedure, obstructive uropathy
  - Levofloxacin or trimethoprim-sulfamethoxazole—for enterics
- If risk for sexually transmitted infection
  - And NO insertive anal intercourse, recent urologic procedure, or urologic obstruction
    - Ceftriaxone—for *N. gonorrhoeae*
    - Doxycycline (azithro as alternative)—for *C. trachomatis*
  - And YES, insertive anal intercourse, recent urologic procedure, or urologic obstruction
    - Ceftriaxone—for *N. gonorrhoeae*
    - Fluoroquinolone (can cover for chlamydia)—for enterics
- For all: scrotal elevation and cold packs

UpToDate Acute Scrotal Pain in Adults
MMWR Vol. 70, No. 4,2021
Trojian, American Family Physician, 2009

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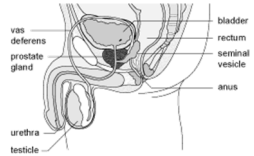
Epididymitis: Management and Complications

- Medical management
  - Antibiotics
  - NSAIDS
  - Scrotal elevation and ice packs
- Complications
  - Testicular infarction
  - Scrotal abscess
  - Epididymo-orchitis



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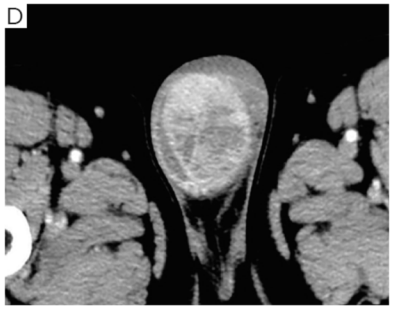
Case #2

- 63-year-old man currently living homeless in Houston presented with a gradually enlarging, painful right testicle over the past 4 months
- Afebrile and he has thickened right scrotal skin but no fistula on exam
- WBC 15,000; negative HIV, AFP, RPR, and beta-HCG
- CT with contrast shows uneven enhancement of right testes and epididymis; the left epididymis was also enlarged with diffuse enhancement

What test would you NOT do next?

A. TB spot
B. Urine culture for AFB
C. Testicular biopsy
D. Urine PCR for TB



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

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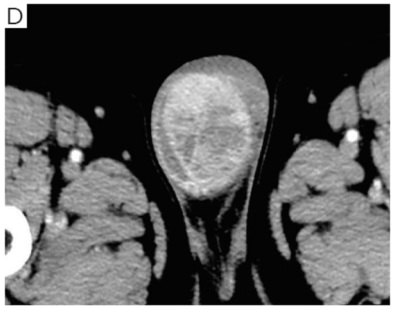
What test would you NOT do next?

A. TB spot
B. Urine culture for AFB
C. Testicular biopsy-contraindicated in germ cell tumor, also can be insensitive/false negative
D. Urine PCR for TB



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

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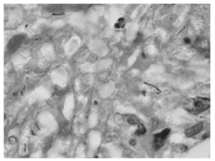
Tuberculous Epididymo-orchitis

- Genitourinary TB typically starts in the epididymis
- Hematogenous or contiguous spread (direct from sexual contact)
- Presents as painful scrotal mass
- Imaging may reveal bilateral involvement
- TB testing often positive
- Diagnosis: AFB stain, culture, and PCR of urine
  - Consider also prostatic secretions
- Avoid fine needle biopsy if any concern for germ cell tumor
- Fistulas, abscesses, and infertility can result if untreated



Yadav et al, Transl Androl Urol 2017
Liu et al, Surgical Infections 2021
Li et al, Quant Imaging Med Surg 2021

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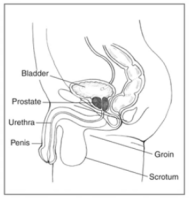
Prostatitis NIH Consensus Categories

- I Acute bacterial* prostatitis
- II Chronic bacterial* prostatitis
- III Chronic prostatitis/chronic pelvic pain syndrome
  - IIIA Inflammatory
  - IIIB non-inflammatory
- IV Asymptomatic inflammatory prostatitis
  - Incidental finding, no need to treat



*includes non-bacterial pathogens, such as fungal organisms

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Understanding the Prostatitis NIH Consensus Categories

Condition	Bacteriuria	Localized to Prostate	Abnormal Rectal Exam	Systemic Illness
I Acute Bacterial Prostatitis	+	+	+	+
II Chronic Bacterial Prostatitis	+	+	+/--	–
III Chronic Pelvic Pain Syndrome	–	–	–	–
IV Asymptomatic Inflammatory Prostatitis	–	–	+/--	–

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

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Understanding the Prostatitis NIH Consensus Categories

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McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

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Case #3

A 69-year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He has chills and nausea in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

What should management should include?

A. Nitrofurantoin
B. Urology consultation for catheterization
C. Culture of expressed prostatic secretions
D. PSA (prostate specific antigen) levels

21

Case #3

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What should management should include?

A. Nitrofurantoin – doesn't penetrate tissue or help with bacteremia
B. Urology consultation for catheterization – may need suprapubic, or transurethral placed with care
C. Culture of expressed prostatic secretions-do not massage the prostate firmly as this may cause bacteremia
D. PSA (prostate specific antigen) levels – will be elevated, non-specific

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Acute Bacterial Prostatitis: Clinical Presentation

- Acutely ill patient
- Prostatic tenderness is the distinguishing featu
- Fever, chills, irritative urinary symptoms
- Lower abdominal, rectal, or perineal pain
- Voiding difficulties
- Pathogenesis: from infection in the urinary tract, prostate biopsy, or hematogenous spread
- Risk factors: urinary catheters, urinary stasis, urinary instrumentation

UpToDate Acute Bacterial Prostatitis
Brede and Shoskes, Nat Rev Urol 2011

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Infectious Prostatitis: Causative Agents

Acute **> 60% caused by**

- *Escherichia coli*
- *Proteus*
- Other Enterobacterales
- *Pseudomonas*
- Staph, strep, enterococci
- *Salmonella typhi* (HIV)
- Burkholderia (traveler to SE Asia or N. Australia)
- STI: gonorrhea or chlamydia

Chronic or immunocompromised

- Mycobacteria
- Fungal
  - Cryptococcus
  - Histoplasma
  - Aspergillus
  - Coccidioidomycosis
  - Candida
  - Blastomycosis
- Brucella

24

Diagnostic Workup of Prostatitis

- Physical exam
  - Painful prostate
- Urinalysis and urine culture
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Prostate ultrasound, computed tomography (CT) scan, MRI
- Call urology if unable to void

25

Antibiotic Treatment of Acute Bacterial Prostatitis

- Most common pathogens are *E. coli* and other Enterobacterales
  - Microbiologic causes are very diverse
- Acute prostatitis
  - Start broad—cephalosporins, carbapenems, +/-aminoglycoside
  - Treatment duration 2-4 weeks
- Oral options: fluoroquinolones, sulfonamides, tetracyclines, macrolides, fosfomycin all penetrate the prostate
- Chronic prostatitis
  - Duration unclear—4, 6, 12 weeks all reported

Lipsky et al, Clinical Infect Dis 2010
Schaeffer and Nicolle, NEJM 2016
Chou et al, Drugs 2022
Brehm, ID Clin North America 2023
UpToDate Chronic Bacterial Prostatitis

26

Case #4

A 72-year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation.

What is the most common cause of a chronic form of this condition?

A. Herpes
B. Chlamydia
C. E. coli
D. Candida

27

Case #4

A 72-year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation.

What is the most common cause of a chronic form of this condition?

A. Herpes
B. Chlamydia
***C. E. coli* – most likely cause of chronic prostatitis especially given the history of recurrent urinary tract infection**
D. Candida

28

Chronic Bacterial Prostatitis

- Patients not acutely ill
- Recurrent UTI with same organism is common
- The four-glass Mears-Stamey test is cited often
- In practice urologists more often do the two-glass test
  - Urine samples pre/post prostatic massage
  - 10-fold higher bacterial counts post massage

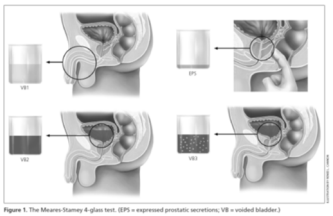

Figure 1. The Meares-Stamey 4-glass test. (EPS = expressed prostatic secretions; VB = voided bladder.)

Sharp et al, Am Fam Physician 2010

29

Case #5

A 58-year-old man presents with fever and shaking chills the day after undergoing transrectal prostate biopsy for possible prostate cancer. Prior to the biopsy, he had received one dose of oral ciprofloxacin. He was treated with trimethoprim-sulfamethoxazole for a UTI 3 months prior.

In the emergency department, his temperature is 101.5, and he has rigors. He reports rectal pain and difficulty voiding. His creatinine is normal. Blood and urine cultures are sent.

Which of the following antibiotics would be <u>the best empiric choice</u>?

A. Amikacin
B. Fosfomycin
C. Ciprofloxacin
D. Trimethoprim-sulfamethoxazole

30

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In the emergency department, his temperature is 101.5, and he has rigors. He reports rectal pain and difficulty voiding. His creatinine is normal. Blood and urine cultures are sent.

Which of the following antibiotics would be <u>the best empiric choice</u>?

A. **Amikacin-** reasonable choice with normal renal function. Carbapenems and 3rd generation cephalosporins also reasonable.
B. Fosfomycin-does not reach adequate levels in bloodstream
C. Ciprofloxacin-the organism is presumably resistant
D. Trimethoprim-sulfamethoxazole – too risky in suspected bacteremia given widespread *E. coli* resistance, especially with recent exposure to TMP/SMX

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Antibiotic Prophylaxis for Prostate Biopsy

- Strongly recommended
- Pre-procedure antibiotics reduce the risk of bacteriuria, symptomatic UTI, bacteremia, fever, acute prostatitis, hospitalization
- No one best choice
- Options include fluoroquinolones, TMP/SMX, gentamicin, and ceftriaxone
- One dose, one hour to the procedure
- No benefit seen for enemas prior to procedure
- Infection after biopsy often caused by fluoroquinolone-resistant *E. coli*

Zani et al, Cochrane Review, 2011

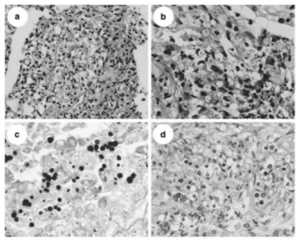
32

Case #6

A 55-year-old man with HIV/AIDS (CD4 32) was referred to urology for obstructive voiding symptoms. Prostate exam revealed asymmetric enlargement. Urinalysis and urine culture unremarkable. Ultrasound showed bilateral nodules consistent with malignancy.

What did the biopsy reveal?

A. Candida
B. E. coli
C. Cryptococcus
D. Aspergillus
E. Nocardia



Wada et al, Prostate Cancer and Prostatic Dis 2008
Adams et al, Urology 1992
Wise and Shteynshlyuger, Curr Urology Rep 2006

33

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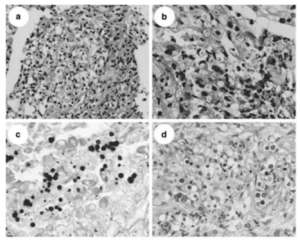

Wada et al, Prostate Cancer and Prostatic Dis 2008
Adams et al, Urology 1992
Wise and Shteynshlyuger, Curr Urology Rep 2006

34

Case #7

A 35-year-old man who is a member of a religious group that does not support vaccination attended a wedding in Nebraska. Two days later he developed pain in his left ear and jaw tenderness. Eleven days later he had noticeable swelling under both sides of his jaw, fever, and painful swelling of his left testicle.

What is the likely causative agent?

A. Mumps
B. Measles
C. Escherichia coli
D. Neisseria gonorrhea

35

Case #7

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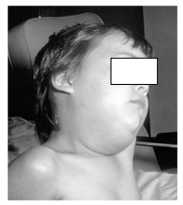
What is the likely causative agent?

A. Mumps-parotid swelling and orchitis
B. Measles
C. Escherichia coli
D. Neisseria gonorrhea



https://www.scientificamerican.com/article/a-mumps-outbreak-among-fully-vaccinated-people/
https://www.cdc.gov/mumps/about/photos.html

36

Orchitis (Isolated Involvement of Testes)

- Viral infections are common
  - Mumps
  - Coxsackie B
  - Lymphocytic choriomeningitis
- Bacterial
  - Contiguous spread from epididymis
  - Same organisms as epididymitis
    - *E. coli* and other enterics
    - Also, same rare organisms (TB, fungal)

https://www.environmentandsociety.org/arcadia/mumps-post-secondary-environment-targeted-advertising-2007-2008-alberta-mumps-vaccination

37

Mumps in the United States

https://www.cdc.gov/mumps/outbreaks/index.html

- Rising since 2006
- Outbreaks in communities with close contact
- Vaccine effectiveness 88% for 2 doses
- PCR testing more reliable than IgG and IgM

Lam, et al. Mumps, Clin Microbiol Rev 2020

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To Wrap Up:

- Epididymitis
  - Consider sexually transmitted infection versus *E. coli* and other enteric flora
- Prostatitis
  - Consider acute bacterial prostatitis in men with febrile UTI – detected by physical exam
  - Consider chronic bacterial prostatitis in men with recurrent or relapsing UTI
- Fungal, TB, and other indolent organisms (Brucella) can invade and infect the male genitourinary tract
- Isolated orchitis is rare in adults – consider viral etiology

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Is Everything Clear Now?

- trautner@bcm.edu
- @bwtrautner

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Online Only Lectures

OL10

Treating Antimicrobial Resistant Infections III Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia

Pranita Tamma, MD

Treating Antimicrobial Resistant Infections III *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*

Pranita D. Tamma, MD, MHS

Johns Hopkins University School of Medicine
Professor, Pediatrics

1

Objectives

- Review the antibiotic treatment for infections caused by:
  - *Pseudomonas aeruginosa* with difficult-to-treat resistance (DTR *P. aeruginosa*)
  - Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
  - *Stenotrophomonas maltophilia*

2

Disclosures

- I have no disclosures.

3

Clinical Infectious Diseases

IDSA GUIDELINES

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

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

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

Provides guidance on the treatment of:

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

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

4

DTR *Pseudomonas aeruginosa* Infections

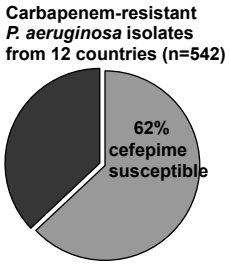
5

P. aeruginosa with Difficult-to-Treat Resistance: Definition

6

P. aeruginosa with Difficult-to-Treat Resistance: Definition

- *P. aeruginosa* exhibiting in vitro resistance to all the following:
  - Piperacillin-tazobactam
  - Ceftazidime
  - Cefepime
  - Aztreonam
  - Meropenem
  - Imipenem-cilastatin
  - Ciprofloxacin
  - Levofloxacin

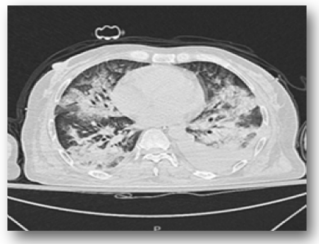


Kadri SS, et al. Clin Infect Dis 2018; 67: 1803-14. Gill CM, et al. Antimicrob Ag Chemother 2021;65:e0120421. Khalili Y, et al. Acta Microbiol Immunol Hung. 2019;66:529-540. Campana EH, et al. Braz J Infect Dis. 2017;21:57-62. Zeng ZR, et al. Diagn Microbiol Infect Dis. 2014;78:268-270.

7

Clinical Case

- 12-year-old male with acute myelogenous leukemia
  - Absolute neutrophil count = 0 cells/mL
- Developed acute onset fevers and respiratory distress
  - Multifocal pneumonia
- DTR *P. aeruginosa* recovered from bronchoalveolar lavage fluid



8

Antibiotic	MIC	Interpretation
Amikacin	> 8 µg/mL	R
Aztreonam	> 16 µg/mL	R
Cefepime	> 16 µg/mL	R
Ceftazidime	> 16 µg/mL	R
Ciprofloxacin	> 2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	> 8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin/tazobactam	> 64/4 µg/mL	R
Tobramycin	> 8 µg/mL	R

Applying Clinical and Laboratory Standards Institute (CLSI) susceptibility criteria

9

β-Lactam Landscape for DTR Infections

Agents (United States FDA-approval year)	Carbapenem-Resistant Enterobacterales			*Pseudomonas aeruginosa* with difficult-to-treat resistance	Carbapenem-resistant *Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
	KPCs	MBLs (NDM, VIM, IMP)	OXA-48-like			
Ceftolozane-tazobactam (2014)						
Ceftazidime-avibactam (2015)						
Meropenem-vaborbactam (2017)						
Cefiderocol (2019)						
Imipenem-cilastatin-relebactam (2020)						
Sulbactam-durlobactam (2023)						
Aztreonam-Avibactam (2025)						

10

Comparing Clinical Outcomes Across Agents

Agent	Survival (generally day 30)	Notes
Ceftolozane-tazobactam	80%	Observational data (n=100)
Ceftazidime-avibactam	83%	Observational data (n=84)
Imipenem-relebactam	90%	Subgroup of clinical trial (n=16)
Cefiderocol	65%	Subgroup of clinical trial (n=101)

Pogue JM, et al. Clin Infect Dis. 2020; 11;71:304-310. Hareza DA, et al. Antimicrob Ag Chemother. 2024;68:e0090724.. Motsch J, et al. Clin Infect Dis. 2020;70:1799-1808. Bassetti M, et al. Lancet Infect Dis. 2021;21(2):226-240.

11

Emergence of Resistance to Cephalosporin-Based Agents

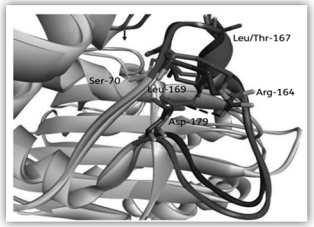
- 28 consecutive patients with DTR *P. aeruginosa* isolates susceptible to ceftolozane-tazobactam and treated with ≥72 hours of ceftolozane-tazobactam
  - *P. aeruginosa* isolates available before and after ceftolozane-tazobactam exposure for broth microdilution testing and sequencing
- **50%** of isolates developed **ceftolozane-tazobactam** resistance
- **86%** of isolates initially susceptible to ceftazidime-avibactam developed resistance to **ceftazidime-avibactam**
- **25%** of isolates initially susceptible to cefiderocol developed ≥4-fold increases in **cefiderocol** MICs

Tamma PD, et al. Clin Infect Dis 2021;73:e4599-e4606. Simner PJ, et al. Open Forum Infect Dis. 2021;8:ofab311.

12

Emergence of Resistance to DTR *P. aeruginosa* Agents

- **Ceftolozane-tazobactam & ceftazidime-avibactam**
  - Resistant mutants most commonly emerge because of amino acid changes in the *Pseudomonas*-derived cephalosporinases [**PDCs**], commonly referred to as "the pseudomonal AmpCs"



13

Clinical Case

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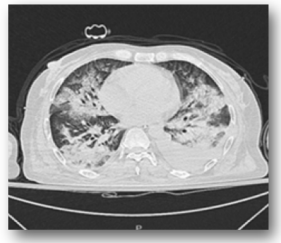


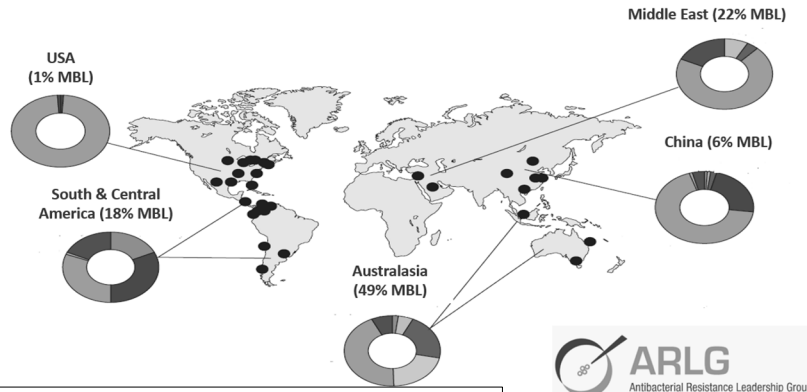
14

Antibiotic	MIC	Interpretation
Amikacin	>8 µg/mL	R
Aztreonam	>16 µg/mL	R
Cefepime	>16 µg/mL	R
Cefiderocol	0.25 µg/mL	S
Ceftazidime	>16 µg/mL	R
Ceftazidime-avibactam	256 µg/mL	R
Ceftolozane-tazobactam	256 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	2 µg/mL	I
Gentamicin	>8 µg/mL	R
Imipenem-relebactam	>8 µg/mL	R
Meropenem	8 µg/mL	R
Piperacillin-tazobactam	>64/4 µg/mL	R
Tobramycin	>8 µg/mL	R

Identified as containing a *bla*$_{VIM}$

15

MBL-Producing *P. aeruginosa* Globally



Reyes G, et al Lancet Microbe. 2023;4:e159-170.

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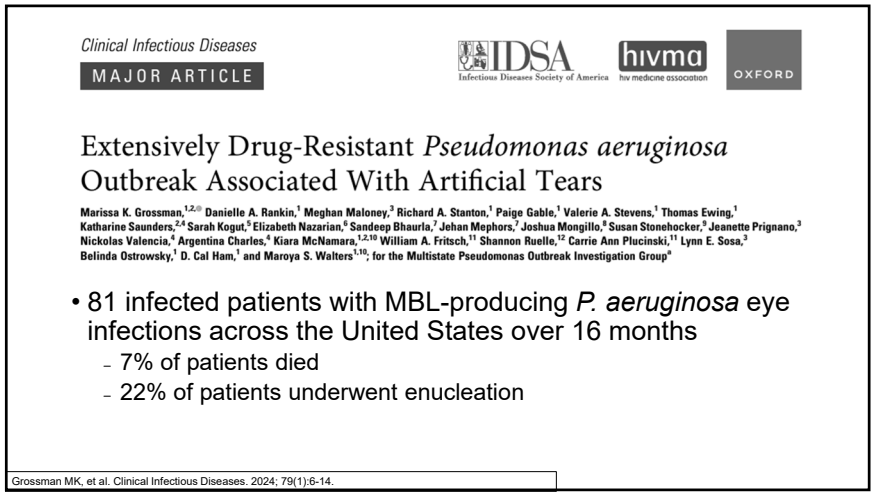

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Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

Antibiotic	Likelihood of activity for index infection	Optimal clinical outcomes	Likelihood of activity for subsequent infection	Serious adverse events
Ceftolozane-tazobactam				
Ceftazidime-avibactam				
Cefiderocol				
Imipenem-cilastatin-relebactam				

Green = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution

18

Take-Home Points: DTR *P. aeruginosa*

- Pros and cons to each of the new β-lactams with activity against DTR *P. aeruginosa*
  - Work with your microbiology laboratory to have a system in place to test multiple agents
  - Select a susceptible agent (**ceftolozane-tazobactam**, **ceftazidime-avibactam**, **imipenem-relebactam** > **cefiderocol**, if active)
  - Request retesting of susceptibilities for subsequent DTR *P. aeruginosa* isolates
- MBL-producing *P. aeruginosa*
  - Hint: Resistant to all currently available BL/BLIs
  - **Cefiderocol** preferred

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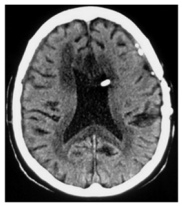
Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections

20

Clinical Case

- 42-year-old women with ventriculoperitoneal (VP) shunt dependency for congenital hydrocephalus
- VP shunt removal and external ventricular drain (EVD) placement scheduled after elective intra-abdominal surgery
- 6 days after EVD placement presents with fevers, headache, and generally ill appearance
- Culture of the cerebrospinal fluid growing CRAB



Tamma PD, et al. Clin Infect Dis. 2024; doi: 10.1093/cid/ciae210.

21

Antibiotic	MIC	Interpretation
Amikacin	>32 µg/mL	R
Ampicillin-sulbactam	>16/8 µg/mL	R
Ceftazidime	>16 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	≤1 µg/mL	I
Cefepime	>16 µg/mL	R
Gentamicin	>8 µg/mL	R
Meropenem	>8 µg/mL	R
Tobramycin	>8 µg/mL	R
Trimethoprim/sulfamethoxazole	>2/38 µg/mL	R

22

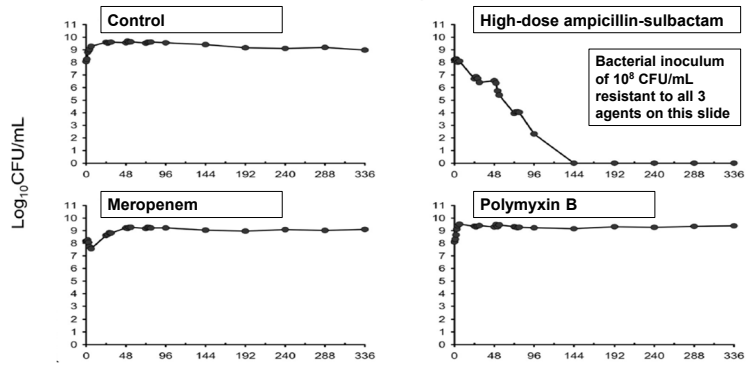
Benefits of Sulbactam

- Ability to function as a β-lactam and can saturate **PBP1a/1b** and **PBP3** of *A. baumannii* isolates
- Unique activity against *A. bauma*nnii isolates demonstrated through in vitro studies, animal models, and clinical outcomes data

Lenhard JR, et al. Antimicrob Agents Chemother. 2017;61:e01268-01216. Beganovic M, et al. Antimicrob Agents Chemother. 2021;65:e01680-01620. Abdul-Mutakabbir JC, et al. Antibiotics (Basel). 2021;10. Rodriguez-Hernandez MJ, et al. J Antimicrob Chemother. 2001;47:479-482. Makris D, et al. Indian J Crit Care Med. 2018;22:67-77. Betrosian AP, et al. Scand J Infect Dis. 2007;39:38-43. Assimakopoulos Sfet al. Infez Med. 2019;27:11-16. Liu J, et al. J Glob Antimicrob Resist. 2021;24:136-147. Jung SY, et al. Crit Care. 2017;21:319.

23

Hollow Fiber Infection Model



Lenhard JR, et al. Antimicrob Ag Chemother. 2017;61:e01268-16.

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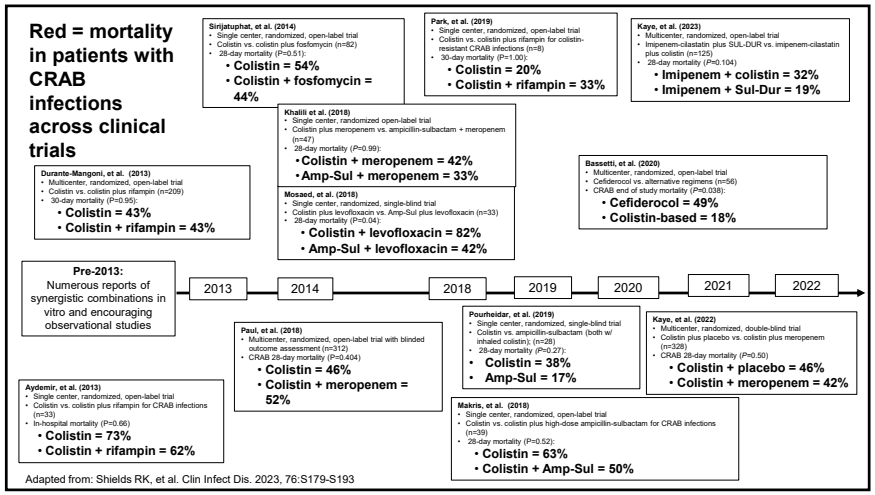

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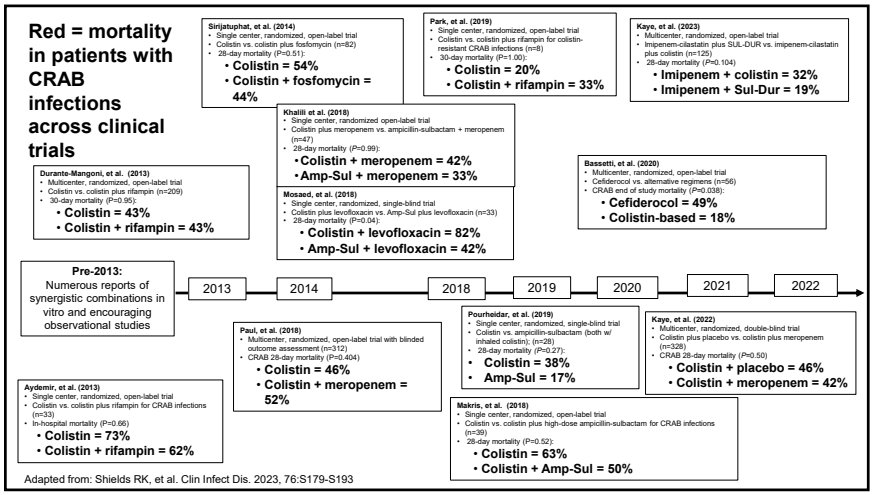


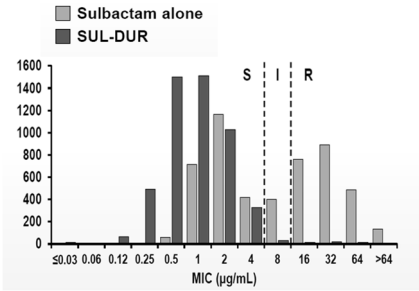
26

Sulbactam-Durlobactam (Sul-Dur)

27

Sulbactam-Durlobactam (Sul-Dur)

- Durlobactam is β-lactamase inhibitor that inhibits class D β-lactamases (e.g., OXA-23)
- Does **NOT** inhibit class B β-lactamases (e.g., NDM)
- 98% of isolates with MIC of ≤4/4 µg/mL (i.e., susceptible) against 5,032 *A. baumannii* isolates



Karlowsky JA, et al. Antimicrob Ag Chemother. 2022;e007812.

28

THE LANCET

Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

29

181 adults with *A. baumannii* pneumonia or bloodstream infections

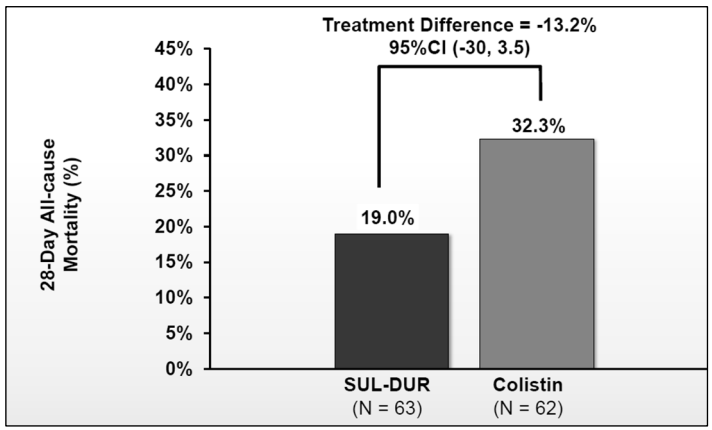
Sul-Dur
(1 gram sulbactam and 1 gram durlobactam)
every 6 hours, over 3 hours
PLUS
Imipenem-cilastatin
(1 gram every 6 hours, over 1 hour)
for 7-14 days

Colistin
(2.5 mg/kg every 12 hours, over 0.5 hours)

PLUS
Imipenem-cilastatin
(1 gram every 6 hours, over 1 hour)
for 7-14 days

Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

30



Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

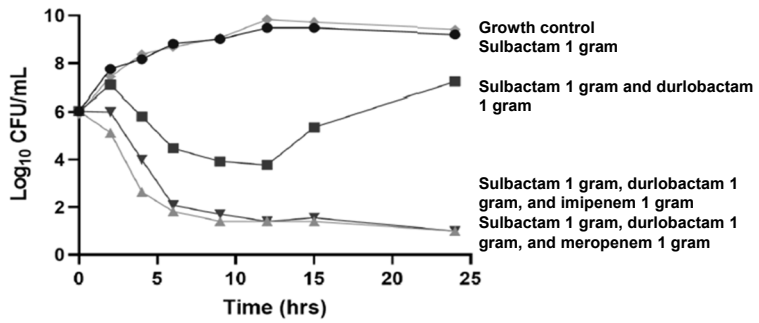
31

Do We Need the Imipenem-Cilastatin?

- Studies suggest the combination of sulbactam-durlobactam and imipenem-cilastatin lowers the sulbactam-durlobactam MIC by ~1-2-fold
  - For example, 4/4 µg/mL to 2/4 µg/mL or 1/4 µg/mL
  - Similar impact with meropenem
- Hypotheses
  - Targeting of multiple PBPs; sulbactam binds to PBP1 and PBP3; carbapenem binds to PBP2, both under protection of durlobactam

O'Donnell J, et al. Antimicrob Agents Chemother 2024;68:e0031223. Iovleva A, et al. mBio 2022;13:e0275921. Choi JY, et al. Clin Microbiol Infect 2004;10:1098-101.

32



O'Donnell J, et al. Antimicrob Agents Chemother 2024;68:e0031223.

33

THE LANCET

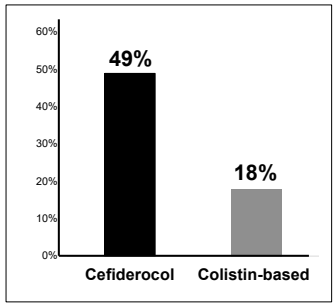
Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

Bassetti M, et al. Lancet Infect Dis. Lancet Infect Dis. 2021;21:226-240.

34

End of Study Mortality for 54 Patients with CRAB infections

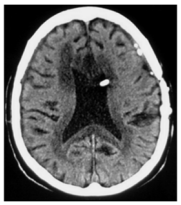


Bassetti M, et al. Lancet Infect Dis. Lancet Infect Dis. 2021;21:226-240.

35

Clinical Case

- 42-year-old women with ventriculoperitoneal (VP) shunt dependency for congenital hydrocephalus
- VP shunt removal and external ventricular drain (EVD) placement scheduled after elective intra-abdominal surgery
- 6 days after EVD placement presents with fevers, headache, and generally ill appearance
- Culture of the cerebrospinal fluid growing CRAB



36

- **Day 1-10:** EVD replaced; received cefiderocol and high-dose Amp-Sul (CSF cultures remained positive)
- **Day 11:** Sul-Dur and meropenem initiated and continued for 14 days; no further positive cultures after this regimen began; remains clinically well 6 months out

Antibiotic	MIC	Interpretation
Amikacin	>32 µg/mL	R
Ampicillin-sulbactam	>16/8 µg/mL	R
Cefiderocol	0.25 µg/mL	S
Ceftazidime	>16 µg/mL	R
Ciprofloxacin	>2 µg/mL	R
Colistin	≤1 µg/mL	I
Cefepime	>16 µg/mL	R
Gentamicin	>8 µg/mL	R
Meropenem	>8 µg/mL	R
Sulbactam-durlobactam	--	S
Tobramycin	>8 µg/mL	R
Trimethoprim-sulfamethoxazole	>2/38 µg/mL	R

Tamma PD, et al. Clin Infect Dis. 2024; doi: 10.1093/cid/ciae210.

37

Take-Home Points: CRAB

- Identification of CRAB in a clinical specimen does not always mean antibiotic therapy is indicated
- Sulbactam-based regimens remain the cornerstone of treatment
  - First choice: **Sul-Dur** (with imipenem or meropenem)
  - Second choice: **High-dose Amp-Sul** (with an additional agent)
- Potential "additional agents" include **polymyxin B** or **minocycline** or **cefiderocol**

38

Stenotrophomonas maltophilia Infections

39

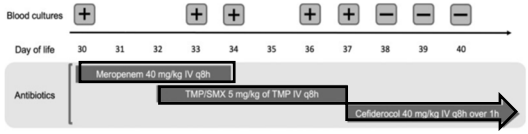
Antibiotics I will be Discussing

- Trimethoprim-sulfamethoxazole (TMP-SMX)
- Cefiderocol
- Ceftazidime-avibactam & aztreonam (i.e., aztreonam-avibactam)
- Minocycline
- Levofloxacin

40

Clinical Case: *S. maltophilia*

- 30-day-old with transposition of great arteries
- Arterial switch operation on day 5, ECMO post-operatively, awaiting cardiac transplant
- Persistent *S. maltophilia* bacteremia
- Trimethoprim-sulfamethoxazole (TMP-SMX) susceptibility confirmed with broth microdilution (i.e., all isolates with MIC ≤2/38 µg/mL)



Hsu AJ, et al. Open Forum Infect Dis. 2023; 10: ofad174.

41

Brief Overview of *S. maltophilia*

- Present extensively in the environment (e.g., water sources, plant, soil)
- Opportunistic pathogen that colonizes or infects vulnerable hosts usually with underlying dysbiosis (e.g., cystic fibrosis, intensive care unit patients)
- Can cause hemorrhagic pneumonia in patients with hematologic malignancies
  - Attributable mortality over **80%**
  - Each additional day of meropenem increases the risk of *S. maltophilia* infection by **17%** in this population

Mojica MF, et al. JAC Antimicrob Resist. 2022;4:dlac040. Brooke JS. Clin Microbiol Rev. 2012;25:2-41. Paez JI, et al. J Hosp Infect 2008;70:101-8. Karaba SM, et al. Antimicrob Agents Chemother 2021; 65:e0079321. Kim SH, et al. Eur J Clin Microbiol Infect Dis 2019; 38:285–95. Aitken SL, et al. Clin Infect Dis. 2021;72:1507-1513.

42

TMP-SMX: Maybe Not as Reliable for *S. maltophilia* as We Once Believed?

- First used in 1973 in a patient with endocarditis failing gentamicin monotherapy for *S. maltophilia* endocarditis
  - Gradually became mainstay of therapy after this case report
  - >10,000 isolates from 2000-2022: remains active against **~90%** of isolates
  - No clinical trials investigating the role of TMP-SMX for *S. maltophilia* infections
- Difficult to interpret clinical outcomes data of TMP-SMX for *S. maltophilia*
  - Small sample sizes, heterogeneity of sources of infection, unclear if colonization or infection, MIC data missing, delays in initiation of active therapy, etc.
- We are left deriving TMP-SMX efficacy against *S. maltophilia* from pharmacokinetic-pharmacodynamic and animal models

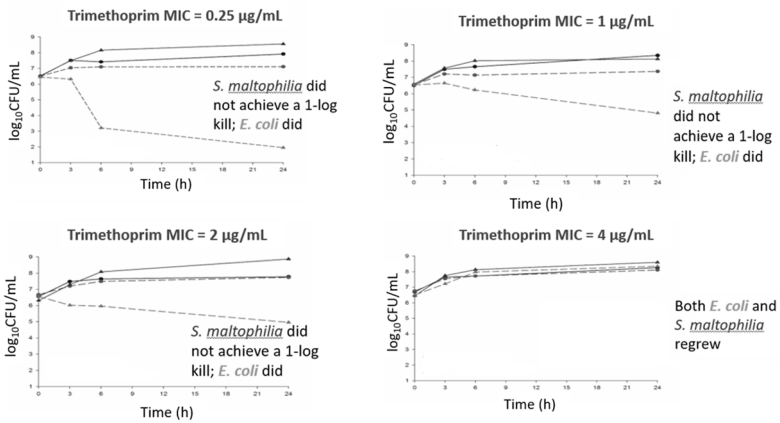
Fischer JJ. J Infect Dis 1973;128:Suppl:771-3. Dadashi M, et al. J Glob Antimicrob Resist 2023;34:253-67. Mendes ET, et al. Rev Inst Med Trop Sao Paulo 2020; 62: e96. Hu LF, et al. J Chemother 2018;30: 25–30.

43

TMP-SMX Breakpoints for *S. maltophilia*

- United States Food and Drug Administration (FDA) has **no breakpoints**
  - Data re-reviewed in 2023 with no changes made
- Clinical and Laboratory Standards Institute has a breakpoint (i.e., MIC TMP ≤2 µg/mL) - recommends TMP-SMX **be used as combination therapy**
  - Data reviewed in 2023; other proposals included (1) removing susceptible category or (2) lowering TMP breakpoint from 2 to 0.5 µg/mL
- European Committee on Antimicrobial Susceptibility Testing (EUCAST) defines **susceptible as TMP MIC ≤0.001 µg/mL** and resistant as >2 µg/mL

44

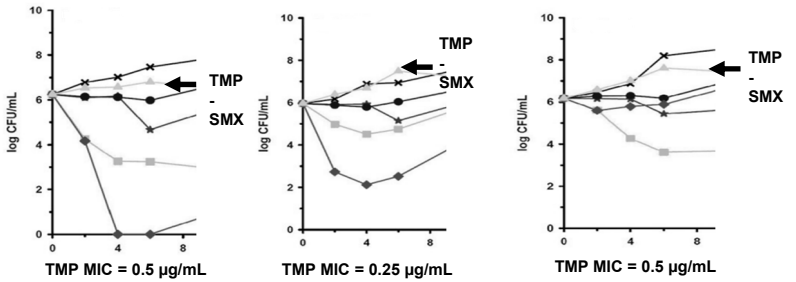


TMP-SMX human simulated dosages equivalent to 20 mg/kg/day

Lasko MJ, et al. Antimicrob Agents Chemother. 2022; 66:e0216721.

45

Additional Time-Kill Experiments



TMP-SMX concentration was 4 times the TMP MIC for 3 TMP-susceptible isolates with no bactericidal activity observed.

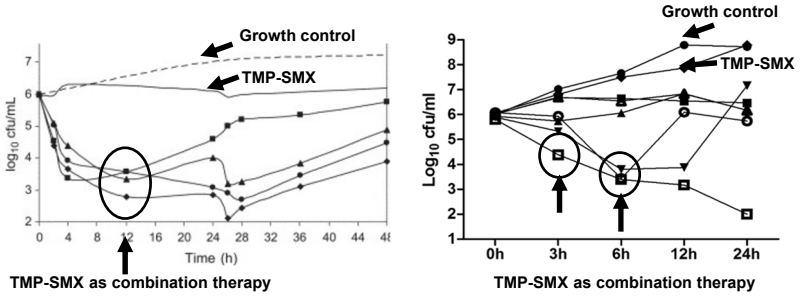
Biagi M, et al. Antimicrob Agents Chemother. 2020;64:e00559-20.

46

Can Combination Therapy Improve the Activity of TMP-SMX?

47

Can Combination Therapy Improve the Activity of TMP-SMX? (Maybe)



Zelenitsky SA, et al. Diagn Microbiol Infect Dis. 2005;51:39-43. Wei C, et al. PLoS One. 2016;11:e0152132.

48

Results from Monte Carlo Simulations

TMP-SMX 10 mg/kg/day	*S. maltophilia* stasis	*E. coli* stasis
TMP MIC 0.5 µg/mL	**96%**	100%
TMP MIC 1 µg/mL	12%	84%
TMP MIC 2 µg/mL	0%	2.5%
TMP-SMX 15 mg/kg/day	***S. maltophilia* stasis**	***E. coli* stasis**
TMP MIC 0.5 µg/mL	**100%**	100%
TMP MIC 1 µg/mL	71.1%	99.6%
TMP MIC 2 µg/mL	0.8%	39.8%

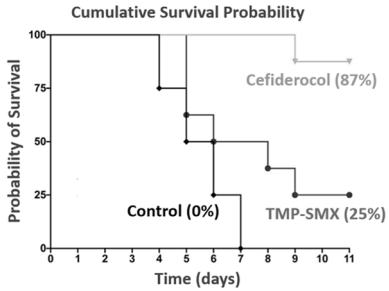
Derived from Cheng AC, et al. Antimicrob Agents Chemother. 2009;53:4193-9. Chin TW, et al. Antimicrob Agents Chemother.1995;39:28-33.

49

TMP-SMX & *S. maltophilia* in a Rabbit Model

Response of *S. maltophilia* pneumonia in neutropenic rabbits treated with:

- **No antibiotics** (n=8)
- **TMP-SMX** (n=8)
- **Cefiderocol** (n=8)



Note: Due to high natural thymidine levels in mice, murine models not suitable for TMP-SMX evaluations. Serine thymidine levels in rabbits comparable to humans.

Petraitis V, et al. Antimicrob Agents Chemother. 2022;66:e0061822.

50

Cefiderocol Clinical Data

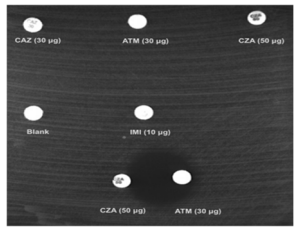
- Clinical trial comparing cefiderocol versus colistin-based regimens
  - All 5 patients with *S. maltophilia* infections randomized to cefiderocol arm
  - Treatment response for the 5 cases categorized as "indeterminant" with 4 of the 5 patients not surviving
- Several case reports suggest clinical success associated with use of cefiderocol for refractory *S. maltophilia* infections

Bassetti M, et al. Lancet Infect Dis 2021;21:226–40. Hsu AJ, et al. Open Forum Infect Dis. 2023; 10: ofad174. Frantoni AJ, et al. Int J Antimicrob Agents. 2021;58:106395. Falcone M, et al. Clin Infect Dis. 2021;72:2021-2024. Zappulo E, et al. Ann Hematol. 2022;101:2805-2806. Koirala A, et al. Pediatr Infect Dis J. 2023;42:1012-1016.

51

Aztreonam-Avibactam

- *S. maltophilia* is intrinsically resistant to most β-lactams because of two chromosomally encoded inducible β-lactamases
  - LI metallo-β-lactamase **(Aztreonam)**
    - Class B3 metallo-β-lactamase
  - L2 cephalosporinase **(Avibactam)**



Evidence of synergy between aztreonam & avibactam

Mojica MF, et al. Antimicrob Agents Chemother 2016; 60:5130-5134. Mojica MF, et al. Antimicrob Agents Chemother. 2017;61:e00777-17. Poeylaut-Palena AA, Bioorg Med Chem Lett. 2007;17:5171-4.

52

Activity of Aztreonam-Avibactam Against *S. maltophilia*

- Aztreonam-avibactam active against **~90%** of *S. maltophilia* isolates
- Reduced aztreonam-avibactam susceptibility associated with increased expression of genes encoding **LI metallo-β-lactamase** and **efflux pumps**

Biagi M, et al. Antimicrob Agents Chemother 2020; 64:e00297-20. Mojica M, et al. Antimicrob Agents Chemother 2017; 61:e00777-17. Lin Q, et al. BMC Microbiology 2021; 21:60. Sader HS, et al. Antimicrob Agents Chemother 64:e01433-20.

53

Aztreonam-Avibactam Clinical Data

- Clinical trial to compare efficacy of aztreonam-avibactam versus alternative therapy for invasive MBL-producing infections
  - Only 3 patients with *S. maltophilia* infections
  - All randomized to aztreonam-avibactam
  - Outcomes: 1 favorable, 1 indeterminate, 1 unfavorable
- Several case reports suggest clinical success associated with use of aztreonam-avibactam for refractory *S. maltophilia* infections

ClinicalTrials.gov Identifier: NCT03580044. Mojica MF, et al. Antimicrob Agents Chemother 2016; 60:5130-5134. Diarra A, et al. Infect Dis Now. 2021 Oct:637-638. Torres ND, et al. J Infect Dev Citries. 2023;17:881-885.

54

Minocycline

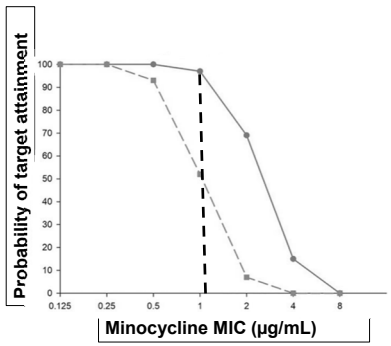
- CLSI lowered minocycline breakpoints against *S. maltophilia* from ≤4 µg/mL to ≤1 µg/mL in 2024
- Applying new CLSI breakpoints, *S. maltophilia* susceptibility to minocycline ranges from ~35% to 90%
- *S. maltophilia* resistance to minocycline generally mediated by upregulation of several intrinsic multidrug-resistant efflux pumps

Mojica MF, et al. JAC Antimicrob Resist 2022;4:dlac040. Bakthavatchalam YD, et al. Eur J Clin Microbiol Infect Dis 2024;43:2453-7. Crowley PD, et al. Eur J Clin Microbiol Infect Dis. 2025;44:459-460. Wei C, et al. PLoS One 2016; 11: e0152132.

55

Minocycline PK-PD Data

- Monte Carlo simulations indicate minocycline dosages of 200 mg IV every 12 hours have a **>90%** probability of achieving PK/PD targets associated with **bacterial stasis** in a neutropenic mouse thigh model for organisms with **MICs of 1 µg/mL**
  - **50%** probability of achieving targets associated with **1-log kill**
- Reasonable to use oral minocycline at same dose



Frantoni AJ, et al. J Antimicrob Chemother. 2022;77:1052-1060.

56

Levofloxacin

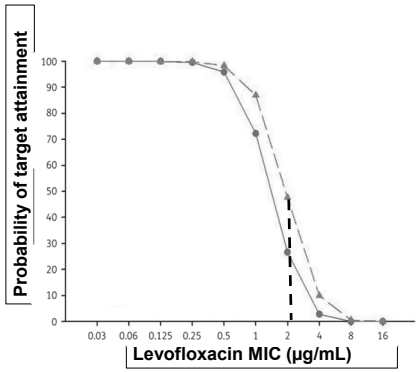
- CLSI has a susceptibility breakpoint of MIC ≤2 µg/mL
- Susceptibility against approximately 80% of *S. maltophilia* isolates from South and North America
- Resistance to levofloxacin associated with overexpression of efflux pumps & a chromosomally encoded Sm*qnr* gene that protects gyrase and topoisomerase from levofloxacin
  - Upon exposure to levofloxacin, Sm*qnr* gene upregulated
- Observational studies indicate emergence of resistance to levofloxacin during therapy generally ranges between 20-50%

Cho SY, et al. Antimicrob Agents Chemother 2014;58:581-3. Nys C, et al. Antimicrob Agents Chemother 2019;63. Sánchez MB, et al. Antimicrob Agents Chemother 2010; 54: 580–1. García-León G, et al. Environ Microbiol 2014;16:1282–96. García-León G, Clin Microbiol Infect 2015;21:464–7.

57

Levofloxacin PK-PD Data

- Monte Carlo simulations indicate levofloxacin dosages of 750 mg IV every 24 hours has a **87%** probability of achieving PK/PD targets associated with **bacterial stasis** in a neutropenic mouse thigh model for organisms with **MICs of 1 µg/mL**
  - **72%** probability of achieving targets associated with **1-log kill**



Frantoni AJ, et al. J Antimicrob Chemother. 2021;77:164-168.

58

Take-Home Points: *S. maltophilia*

- Identification of *S. maltophilia* in a clinical specimen does not always indicate antibiotic therapy is necessary
  - *S. maltophilia* infections in hematologic malignancy patients should be taken seriously
- For severe infections IDSA Guidance suggests **cefiderocol** or **aztreonam-aztreonam** (or combination of ceftazidime-avibactam and aztreonam)
- For non-severe infections a combination of **TMP-SMX**, **minocycline**, or **levofloxacin** are suggested

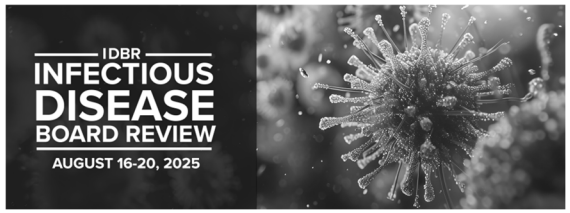
59

Online Only Lectures

OL11

Antibacterial Drugs Not Covered Elsewhere

Douglas Black, PharmD



Antimicrobial Drugs Not Covered Elsewhere: 10 Issues You Might Get Asked About

Douglas Black, PharmD
University of Washington

7/23/2025

1

Disclosures of Financial Relationships with Relevant Commercial Interests:

- Contributing Editor, *The Sanford Guide to Antimicrobial Therapy*

2

Case #1

- A 22-yo woman presets with acute onset chest pain and painful swallowing
- Onset: 2 days ago
- Sharp retrosternal chest pain worsened by swallowing
- No history of reflux or GERD. No fever, cough, or SOB
- UGI endoscopy: Linear ulcerations in mid-esophagus, mucosal erythema, superficial erosions
- Recently began a new antibacterial medication for a skin condition five days ago
- Dx: drug-induced (pill) esophagitis

3

Question #1

Based on the case, which antibacterial do you suspect she was taking?

A. Levofloxacin
B. Cephalexin
C. Linezolid
D. Metronidazole
E. Doxycycline

4

Question #1

Based on the case, which antibacterial do you suspect she was taking?

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5

Pill Esophagitis

- Inflammation or ulceration of the esophageal mucosa caused by direct contact with a drug.
- Symptoms appear hours (even days) after drug ingestion
- Antimicrobial offenders: Tetracyclines, penicillins, TMP-SMX, clindamycin, spiramycin, erythromycin, rifampin, tinidazole, AZT, azithromycin
- Risk factors:
  - Supine position after drug ingestion
  - Inadequate water intake
  - Pre-existing esophageal motility disorders or strictures
  - Older age
  - Large or multiple medications
- Management
  - Discontinue offending agent
  - Sucralfate, PPIs, viscous lidocaine
  - Hydration, soft diet

6

Case #2

- A 76-yo woman presents with acute confusion, hallucinations and tremors that began two days ago.
- PMH: hypertension, hyperlipidemia, CKD (CrCl ≈40 mL/min).
- VS: BP 138/78, HR 84, afebrile.
- Home meds: metoprolol, hydrochlorothiazide, amlodipine, rosuvastatin.
- Head CT: No acute abnormalities. LP: no pleocytosis, glucose and protein are within normal limits.
- Four days ago, began valacyclovir 1 gm q8h for shingles.

7

Question #2

Which of the following is a risk factor for valacyclovir neurotoxicity in this patient?

A. Renal impairment
B. Treatment with hydrochlorothiazide
C. Hyperlipidemia
D. Hypertension
E. Active VZV infection

8

Question #2

Which of the following is a risk factor for valacyclovir neurotoxicity in this patient?

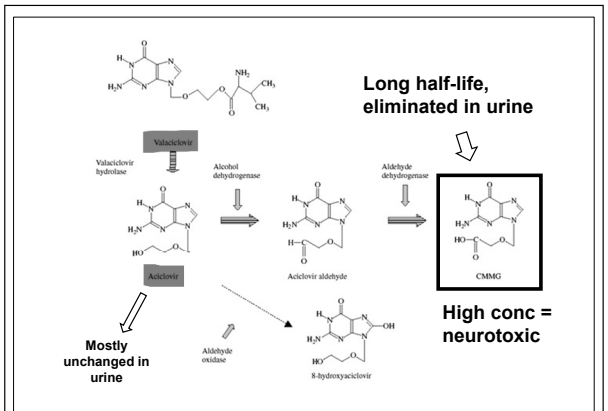
A. **Renal impairment**
B. Treatment with hydrochlorothiazide
C. Hyperlipidemia
D. Hypertension
E. Active VZV infection

9

Valacyclovir Neurologic Toxicity

- Presentation
  - Early: agitation, hallucinations, confusion, disorientation
  - Later: tremor, myoclonus, delirium
  - Rare: seizures, extrapyramidal symptoms
- Key risk factors
  - Renal impairment
  - Age
  - High doses
  - Dehydration
- Pathophysiology: accumulation of CMMG (9-carboxymethoxymethylguanine)
- Management
  - Stop drug
  - Adjust dosage if therapy must be continued
  - Hydration
  - Hemodialysis in extreme cases

10



11

Case #3

- A 9-month-old male infant is brought to the pediatric clinic by his parents due to increased fussiness, poor sleep, and decreased appetite over the past 48 hours. He has been tugging at his right ear.
- He has a low-grade fever (38.3°C) and rhinorrhea. No vomiting or diarrhea.
- ENT exam: Bulging, erythematous right tympanic membrane with reduced mobility on pneumatic otoscopy, mild nasal congestion.
- The family reports difficulty administering liquid amoxicillin in the past due to taste, and they prefer a once-daily dosing option. Cefdinir 14 mg/kg q24h x10 days is chosen.

12

Question #3

What adverse effect specific to cefdinir should the parents be warned about?

A. Serum sickness
B. Brown urine
C. Red stools
D. Skin discoloration
E. Nausea

13

Question #3

What adverse effect specific to cefdinir should the parents be warned about?

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14

Cefdinir-associated Red Stools

- Red or reddish-orange stools occurring in infants and young children. May be interpreted as "bloody diarrhea."
- Cause: cefdinir + iron-fortified infant formula or supplements → non-absorbed complex → red stool
- NOT due to GI bleeding. No abdominal pain or other GI symptoms.
- Typically appears within 1-5 days of starting therapy.
- Can continue the drug, or switch to something else.
- Parent counseling
  - Harmless discoloration
  - Cefdinir therapy should continue
  - Resolves after stopping iron or drug

15

First generation
- Cefazolin
- Oral: cephalexin, cefadroxil

Second generation
- Cefotetan, cefoxitin, cefuroxime
- Oral: cefaclor, cefprozil, cefuroxime axetil

Third generation
- Ceftriaxone, cefotaxime
- Ceftazidime
- Oral: cefpodoxime proxetil, cefdinir, cefixime

Fourth generation
- Cefepime

Fifth generation (covers MRSA)
- Ceftaroline

Others (don't fit well into "generations")
- Cefepime-enmetazobactam, cefiderocol, ceftazidime-avibactam, ceftobiprole, ceftolozane-tazobactam

16

Case #4

- 62-yo man presents with a 3-week history of worsening pain, swelling, and foul-smelling discharge from a chronic ulcer on the plantar aspect of his left foot.
- Treated twice with oral antibiotics in the past, without improvement. Recently developed low-grade fevers and difficulty walking.
- Past medical history: Type 2 diabetes, hypertension, peripheral neuropathy.
- MRI consistent with osteomyelitis involving 1st metatarsal, with adjacent soft tissue gas and abscess formation.
- Wound culture: mixed flora, including anaerobes *(Bacteroides fragilis, Peptostreptococcus)*.
- Plan: surgical debridement, ceftriaxone + metronidazole x6 weeks.

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Question #4

What adverse effect of metronidazole is of most concern in this patient?

A. Nausea
B. Leukopenia
C. Disulfiram reaction
D. Metallic taste
E. Peripheral neuropathy

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Metronidazole-induced Peripheral Neuropathy

- Burning, tingling, numbness in feet/hands (stocking-glove pattern)
- Risk factors
  - Prolonged therapy (> 2-4 weeks)
  - High total dose
  - Pre-existing neuropathy (e.g., diabetes)
  - Other neurotoxic drugs (e.g., vincristine)
- Clinical features
  - Symmetric distal sensory neuropathy
  - ± Mild weakness, gait imbalance
  - Rare: central toxicity (ataxia, encephalopathy)
- Rule out: B12 deficiency, diabetes, alcoholism, other neurotoxins
- Management
  - Stop drug
  - Neuropathic pain meds, PT/OT for gait
- Prognosis
  - Expect recovery in weeks to month
  - Often reversible if recognized early
  - Incomplete recovery if exposure prolonged
- Antimicrobial stewardship
  - Counsel patient on early symptoms if long drug course planned
  - Periodically reassess need for metronidazole

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Case #5

- 65-yo man (5'11", weight 72 kg) is being treated for a forearm infection that has developed purulent drainage over the past few days.
- PMH includes hypertension and a MRSA infection last year.
- Current: T 38.0°C, other VS WNL. WBC 14.8, SCr 1.3 mg/dL (estimated CrCl 60 mL/min).
- Current meds: valsartan, chlorthalidone.
- Decision to incise and drain the wound, then begin TMP-SMX 2 DS tablets q12h until patient is afebrile x3-5 days.
- On the third day, the WBC is WNL, all VS are WNL (he is afebrile), but his SCr has increased to 1.6 mg/dL.

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Question #5

What would be the most reasonable course of action?

A. Continue TMP-SMX at the same dose
B. Continue TMP-SMX at a reduced dose
C. Discontinue TMP-SMX
D. Change to vancomycin IV (15-20 mg/kg IV q12h)
E. Change to dicloxacillin (500 mg PO q6h)

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TMP-SMX-Induced ↑SCr (without affecting glomerular filtration)

- Mechanism: TMP competes with creatinine for tubular secretion.
- Other drugs that can do this: bictegravir, cobicistat.
- Typical increase: around 20% (dose-dependent). So no, we don't expect it to get progressively worse.
- Can be confusing, since TMP-SMX is also actually associated with renal impairment via one of these mechanisms:
  - Acute interstitial nephritis
  - Crystalluria
  - Acute tubular necrosis (rare)
- Another pearl worth remembering: TMP-SMX can result in hyperkalemia
  - TMP acts like amiloride, a K+ sparing diuretic
  - More common at higher doses

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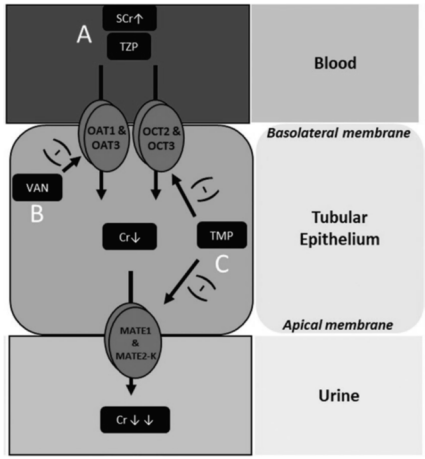

How TMP increases SCr without affecting without affecting glomerular filtration

GLOSSARY
TMP=trimethoprim
Cr=creatinine
OAT=organic anion transporter
OCT=organic cation transporter
MATE=multidrug and toxin extrusion

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Case #6

- 71-yo man presents to the ED complaining of jaundice for two weeks associated with itching and a mild rash involving his limbs and torso. He also mentions his urine is dark brown.
- No fever, headache, myalgias, arthralgias, respiratory symptoms, abdominal pain, nausea, vomiting, diarrhea, anorexia, or weight loss.
- NKA, no recent or distant exposure to alcohol or illicit drugs, non-smoker.
- Abdominal imaging: no relevant findings.
- Lab: hyperbilirubinemia, increased alkaline phosphatase. Mild AST/ALT elevations.
- Two days ago, finished a 14-day course of an antibiotic for a respiratory infection.

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Question #6

Which of the following oral antibiotics (he might have taken) is most associated with drug-induced liver disease?

A. Moxifloxacin
B. Azithromycin
C. Cefuroxime axetil
D. Doxycycline
E. Amoxicillin-clavulanate

27

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Amoxicillin-Clavulanate Induced Liver Disease

- One of the most common causes of drug-induced liver disease (DILI).
- More common than with amoxicillin alone.
- Risk factors: male sex, age >55, alcohol consumption, repeated use of the drug, use of other hepatotoxic drugs.
- Average onset: 3 weeks after initiation of therapy.
- Typical features: fatigue, fever, nausea, abdominal pain, pruritus, jaundice.
- Most common pattern of liver enzyme elevations: cholestatic. A mixed or hepatocellular pattern may be seen in younger patients.
- Usually reversible.

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Case #7

- 65-yo mildly obese man, renal transplant recipient. Immunosuppression regimen includes prednisone. Active lifestyle.
- Estimated CrCl: 45 mL/min.
- Prescribed levofloxacin 750 mg po q24h x14 days for prostatitis.
- After ten days, he complains of bilateral Achilles tendon (AT) pain. He says it began after 3-4 days of levofloxacin. He is switched to TMP-SMX to finish up his therapy.
- AT still painful 4 days later. Prednisone dose increased, apparently to maybe help with the pain.
- One month later, he loses his footing and slips, rupturing his left Achilles tendon.

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Question #7

Which fluoroquinolone is most associated with Achilles tendon rupture?

A. Gemifloxacin
B. Ciprofloxacin
C. Levofloxacin
D. Moxifloxacin
E. Delafloxacin

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Fluoroquinolone and tendons

- Inflammation or rupture of tendons, particularly the Achilles tendon (often bilateral).
- Tendinopathy: incidence 0.14% to 0.4%. Tendon rupture is rare (1-2 per 10,000 patients). Rupture is often preceded by tendinitis, but not always.
- Onset: within days to weeks, may be delayed for a few months.
- Symptoms: tenderness, swelling, stiffness, often accompanied by sharp pain with walking. Symptoms tend to occur acutely.
- Mechanism: unclear.
- Risk factors: See next slide. Statins do not seem to increase the risk.

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FQ tendon rupture	QTc prolongation
Age >60	Older age
Concomitant steroid use	Female gender
Male gender	↑ baseline QT interval
Obesity	Bradycardia
↑cumulative days of FQ exposure	CHF
	Hypokalemia
	Hypomagnesemia
	Other QT-prolonging drugs

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Management of FQ Tendon Injury

- According to the FDA: At the first sign of tendon pain, swelling, or inflammation, patients should stop taking the FQ, avoid exercise and use of the affected area, and promptly contact their health care provider for evaluation and transition to a non-FQ alternative.
- Nonsurgical management strategies for tendinopathy include analgesics, PT, and/or immobilization.
- Surgical intervention may be required in severe cases.
- Most patients recover within a month without debilitating consequences, but in some cases, recovery takes 6 months or longer. Swelling, pain, or difficulty walking may occasionally become long-term complications.

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Case #8

- A 68-yo man (5'10", weight 110 kg) complains of fatigue, easy bruising, and gum bleeding.
- Past medical history includes obesity, type 2 diabetes, hypertension, CKD, and chronic osteomyelitis of his right foot.
- Underwent surgical debridement of his right foot 3 weeks ago.
- SCr 1.6 mg/dL (estimated CrCl 55 mL/min)
- Current meds: linezolid 600 mg po q12h (started at the time of surgery), metformin, lisinopril, and aspirin.
- VS within normal limits. Hemoglobin 9.1 g/dL, hematocrit 27%, WBC 2,100/µL, platelets 62,000 /µL, reticulocytes low. B12, folate normal.

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Question #8

Which of the following is the most important risk factor for linezolid myelosuppression in this patient?

A. Renal impairment
B. Treatment duration >2 weeks
C. Obesity
D. Treatment with lisinopril
E. Diabetes

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Linezolid-induced Myelosuppression

- A reversible pancytopenia
  - Lack of blasts/dysplasia on smear or marrow biopsy
- Risk factors
  - Treatment >14 days (probably most important)
  - Older age
  - Renal dysfunction
  - Concomitant marrow-toxic drugs
- Monitoring recommendation
  - Weekly CBC w/diff for treatment >14 days
- Management
  - Stop drug, switch to alternate agent if necessary
  - Monitor blood counts closely
  - Heme consult if counts continue to decline or fail to recover
  - Recovery expected within 1-2 weeks

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Case #9

- A 63-yo man (73 kg, 5'11") is admitted with worsening back pain.
- Past medical history: type 2 diabetes.
- Allergy: Ceftriaxone (urticaria).
- Blood cultures on admission: *E. faecalis*, pan-sensitive.
- Renal SCr: 1.3 mg/dL (estimated CrCl 62 mL/min).
- TEE: mitral valve vegetation. MRI: L5/S1 vertebral osteomyelitis.
- Treatment proposed: ampicillin 2 gm IV q4h + gentamicin 70 mg IV q8h (both x6-8 weeks).

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Question #9

Which of the following is the most important management concern specific to this patient?

A. Inability to give ampicillin + gentamicin to an outpatient
B. Drug-induced nephrotoxicity
C. Target gentamicin levels are not well-defined in this setting
D. Drug-induced ototoxicity
E. Use of ampicillin in someone with ceftriaxone allergy

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NEPHROTOXICITY	OTOTOXICITY
Reversible	Irreversible
Well defined risk factors*	Poorly defined risk factors
Well defined time course	Poorly defined time course
Monitor SCr	No easy labs to follow
Serum drug concentrations correlate well	Serum drug concentrations correlate poorly

*advanced age, duration of therapy, hypotension, concomitant liver disease, use of other nephrotoxins

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Case #10

- 53-yo man in the ED secondary to a witnessed seizure and loss of consciousness.
- Past medical history: alcohol abuse, seizure disorder.
- Seizures managed, patient treated empirically for meningitis (ceftriaxone 2 gm q12h, ampicillin 2 gm q4h, vancomycin 1 gm q12h, dexamethasone).
- Head CT, LP findings unremarkable. Blood and urine cultures negative. CxR: RLL opacity. On day 2, ceftriaxone continued (same dose), other drugs discontinued. Azithromycin initiated (500 mg IV q24h).
- Day 7: patient jaundiced. Total bilirubin 5.8 mg/dL (↑), direct bilirubin 3.4 mg/dL (↑). Mild RUQ pain.
- RUQ ultrasound: biliary sludge and cholelithiasis, no evidence of cholecystitis.

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Question #10

Which drug is the likely explanation for these observations?

A. Azithromycin
B. Ceftriaxone
C. Vancomycin
D. Ampicillin
E. Dexamethasone

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Ceftriaxone Pseudocholelithiasis

- Drug excreted in bile in high concentrations.
- Can form gallstones consisting of a ceftriaxone-calcium complex (often referred to as biliary sludge). Typically happens around day 9 of treatment.
- Risk factors include:
  - High doses
  - Prolonged therapy
  - Dehydration
  - Receipt of parenteral nutrition
  - Hypercalcemia
- May be more common in children. There are may also be genetic factors.
- Presentation: RUQ tenderness, nausea.
- LFTs: Usually a cholestatic pattern.
- Drug discontinuation usually solves the problem.
- Resolution of sludge can take about 2 weeks.

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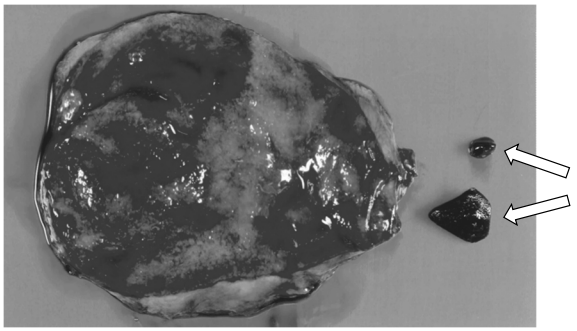

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