# TABLE OF CONTENTS – VOLUME 2


| SECTIONS | PAGE |
|---|---|
| Course Overview | 1 |
| Accreditation, Evaluation & CME Claim Information | 3 |
| Homestudy Course | 4 |
| Online Materials | 5 |

# COURSE OVERVIEW

## ABOUT THE COURSE

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

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

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

## EDUCATIONAL OBJECTIVES

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

## PROGRAM FACILITATORS

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

## CME PROVIDER

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

# ACCREDITATION, CME & MOC CLAIM INFORMATION - PHYSICIANS

## TYPES OF CREDIT

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

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

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

## HOMESTUDY COURSE

### ACCREDITATION

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

### CME CREDIT FOR PHYSICIANS

The George Washington University School of Medicine and Health Sciences designates this enduring activity for a maximum of 43.50 *AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### CLAIMING MOC POINTS

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

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

### DEADLINE FOR CLAIMING MOC POINTS

ABIM Board Certified physicians need to claim MOC points for this course by December 31, 2026, in order for the MOC points to count toward any MOC requirements that are due by the end of 2026.

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

# OVERVIEW AND INSTRUCTIONS FOR CLAIMING CME CREDIT AND MOC POINTS

## COURSE MATERIALS

**LECTURE RECORDINGS**

- Participants can receive CME credits and MOC points by watching/listening to the lecture recordings and completing the daily course evaluations.
- In addition, the archived recordings are organized chronologically by day. You have the option to view them online with the slides, with streaming audio, or you can download the MP3 audio file onto your personal computer or mobile device.

**TO CLAIM CME CREDIT(S):**

- Complete the five (5) session/speaker evaluations.
- Complete the final course evaluation called “Overall Evaluation.”
- Upon completing the final course evaluation, you will be redirected to the link to claim CME credit where you will be asked to check the Attestation Statement box and enter the number of CME credits commensurate with the extent of your participation in the activity.

**TO CLAIM MOC POINT(S):**

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

# ONLINE MATERIALS

## ACCREDITATION

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

## CME CREDIT FOR PHYSICIANS

The George Washington University School of Medicine and Health Sciences designates this enduring material for a maximum of 71.50 *AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## MOC POINTS

Successful completion of this CME activity enables the participant to earn up to 71.50 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program.

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

## CLAIMING MOC POINTS

Participants can earn up to 71.50 hours of CME credit and MOC points by completing the below online activities associated with the course.

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

## DEADLINES FOR CLAIMING MOC POINTS

ABIM Board Certified physicians need to claim MOC points for this course by December 31, 2026, in order for the MOC points to count toward any MOC requirements that are due by the end of 2026.

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

# OVERVIEW OF ONLINE MATERIALS

## CLAIMING CME AND MOC

| ONLINE ONLY LECTURES | CME HOURS: 7.25 | MOC POINTS: 7.25 |
|---|---|---|
| • There are fifteen (15) lectures that feature topics that were not covered in the live course. | | |
| **QUESTION SETS** | **CME HOURS: 56** | **MOC POINTS: 56** |
| • There are five (5) sets of 100 board prep questions.<br>• There is one (1) set of 35 HIV Therapy questions.<br>• You will see the correct answer and rationale after submitting each question.<br>• You can only go in the forward direction when answering questions.<br>• 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.<br>• This PDF reviews information that summarizes important topics in photos, tables, and short summaries. | | |

# GUIDE TO ONLINE MATERIALS ACCESS

## Initial Notification

- If you registered on or before June 14, 2026, you should have received an email confirmation from info@idboardreview.com before or on June 15 with information on accessing the online materials.
- If you register after June 15, 2026, you will receive the access information included in the registration confirmation email.

## Current Access

Instructions for accessing the Online Materials:

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

## Important Links

Please note that you must be logged in to access.

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

**Tuesday, August 25, 2026**

---

**32**

# Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

**Frank Maldarelli, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Clinical Manifestations of Human Retroviral Diseases and Slow Viruses

**Frank Maldarelli, MD/PhD**
**Bethesda, MD**

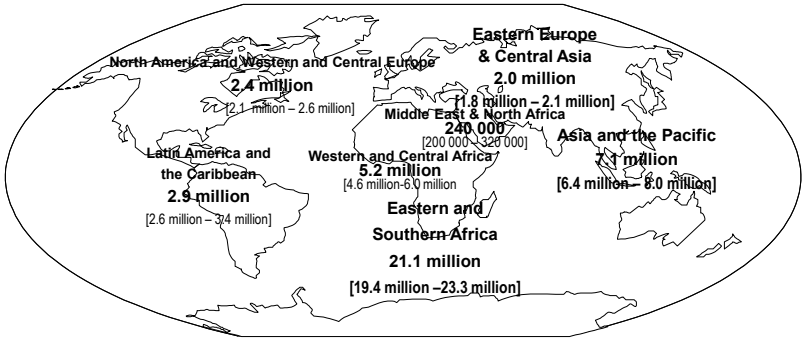
9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Estimated Numbers of Adults and Children with HIV 2025
**HIV prevalence: 40.9 million persons with HIV**

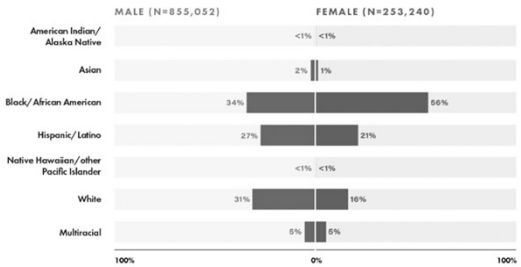



**>75% access to antiretroviral therapy**
**HIV incidence: 1.2 million new infections/year**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

UNAIDS

## 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% |

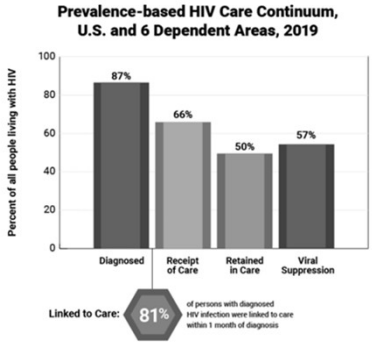
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## 2030 US HIV Public Health Goals: Treatment Cascade

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



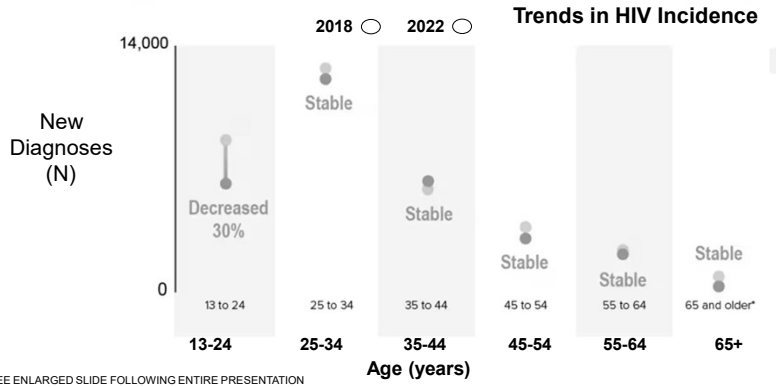

- >50% of Diagnoses are <35
- >50% Living with HIV are >50 years

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

CDC

## 2030 US HIV Public Health Goals: Transmission

**90% Reduction in Incidence by 2030**

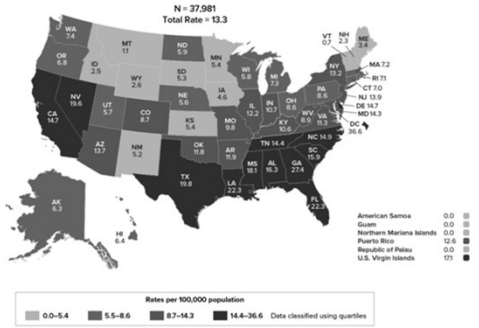



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

CDC

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

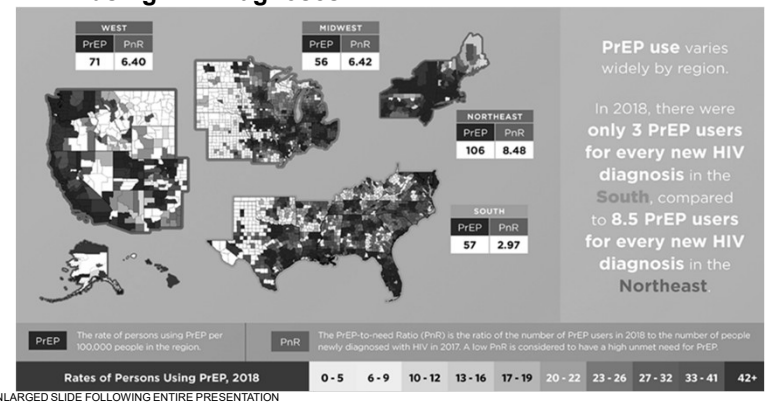
43% all new Diagnoses are in Southeast




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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



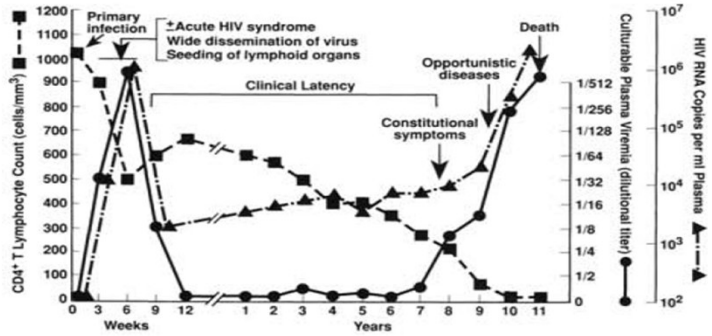

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**32 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**

*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

## HIV Infection Course



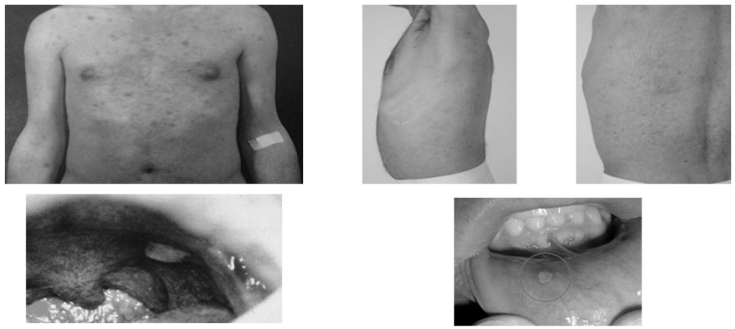

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Acute HIV Syndrome

| | Percent Reporting | | |
|---|---|---|---|
| Sign/Symptom | 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 too work | 1 | 44 | 58 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Primary HIV-1 Infection Syndrome
### Maculopapular Trunk > Extremities



*Enanthem*

*Aphthous ulcer*

## Question #1: HIV Presentation

- A 23-year-old man presents with a history of unprotected receptive anal sex with a 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 antiretroviral therapy is <40 c/ml.


© 2026 Infectious Disease Board Review

## Question #1: HIV Presentation

**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 supplemental 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

## Question #1: HIV Presentation

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

## Early Antiretroviral Therapy

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

## Question #2: HIV Presentation

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

**What would be your answer?**

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


© 2026 Infectious Disease Board Review

## Question #2: HIV Presentation

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

**What would be your answer?**

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

## Long Acting Early Viral Inhibition (LEVI) Syndrome

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

## Question #3: HIV Presentation

- 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

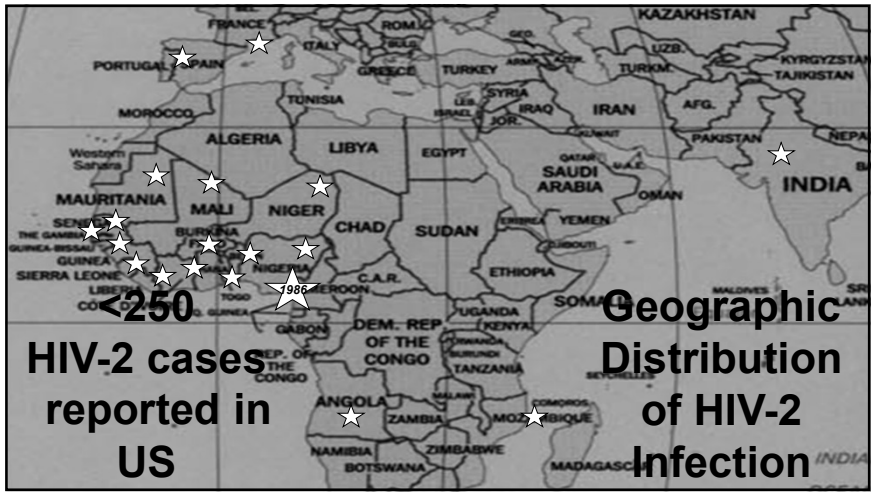
## Question #3: HIV Presentation

- 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


© 2026 Infectious Disease Board Review




## HIV-1 and HIV-2

| Characteristic | HIV-2 | HIV-1 |
|---|---|---|
| **Epidemiology** | | |
| Geography | West/Central Africa | Worldwide |
| Local Distribution | Urban = Rural | Urban > Rural |
| Age-Specific Prevalence | Stable or Decreasing | Increasing |
| **Pathogenesis** | | |
| Average Age at Diagnosis | 45-55 | 20-34 |
| Maternal-Fetal (without RX) | 0-4% | 20-35% |
| Kaposi Sarcoma | Less Common (10X) | More Common |
| **Therapy** | | |
| | NRTI, PI, INSTI, Corec | All Antiretrovirals |
| | **NOT NNRTI, Fusion, (Capsid)** | |
| **Diagnosis** | | |
| Screening | HIV ½ ELISA | HIV ½ ELISA |
| Confirmatory | Supplemental (e.g., Geenius) | Supplemental (Qual HIV RNA) |
| **Monitoring** | | |
| | HIV-2 RNA Assay | HIV-1 RNA Assay |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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

## Question #4

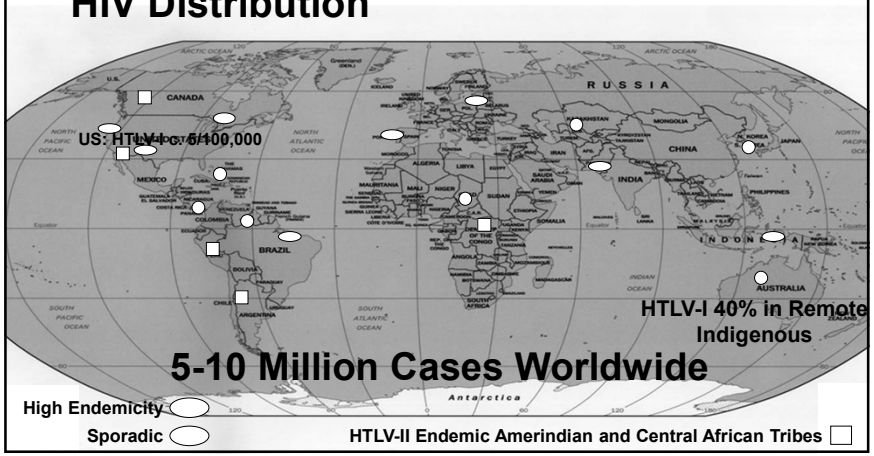
A 25-year-old pregnant woman immigrant from southern Japan was referred to you for evaluation of a positive HTLV-I western blot.

**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

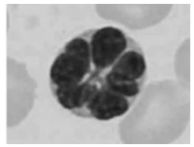

© 2026 Infectious Disease Board Review

## HIV Distribution




## 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

## 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



## 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




© 2026 Infectious Disease Board Review

## HTLV-I Acute T Cell Leukemia (ATL)

**Disease Onset**
- Long Latency (>30 years)
- Small pediatric series in South America

**Epidemiology**
- Approximately 1% of HTLV- I infected adults
- M>F (Japan); M=F (Jamaica)

**Associated syndromes**
- Infectious
  - TB, MAC, Leprosy
  - PCP
  - **Recurrent *Strongyloides***
  - Scabies esp. Norwegian scabies
- Noninfectious-hypercalcemia+lytic bone lesions

**Therapy**
- Cytotoxic chemotherapy
- AZT + Ifn
- Transplant
- Mogamulizumab (Poteligeo, anti-CCR4 monoclonal)
- APPROVED in Japan for ATL
  - In US FDA approved for relapsed or refractory Sezary or mycosis fungoides
- Lenalidamide in trials

## Question #6

- 38-year-old woman from Jamaica presents with weakness, unsteadiness of several months duration and has recently developed incontinence
- Neurologic exam notes hyperreflexia ankle clonus, and positive Babinski reflex
- WBC = 7500 cells/µl
- CD4 T cell = 1000 cells/µl
- CSF cell count: 10 cells/$mm^3$ (lymphocytes)
- CSF protein: 75 mg/dl

## Question #6

**What other condition is the etiologic agent for this illness also associated with?**

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

## Question #6

**What other condition is the etiologic agent for this illness also associated with?**

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


© 2026 Infectious Disease Board Review

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

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

## HTLV-I TSP/HAM

**Presentation**

- Spastic paraparesis
  - Lower > upper
  - Proximal > distal
- Bladder disturbance
- Hyperreflexia
- Positive Babinski reflex

**Differential Diagnosis**

- Cord compression
- B12 deficiency
- Syphilis
- HIV-1 myelopathy
- Multiple sclerosis

## Therapy of HTLV-I TSP/HAM

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

## Question #7

- 62-year-old 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

**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


© 2026 Infectious Disease Board Review

## 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

### 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

## 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 jirovecii
- On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and the hematology technician remarks that some of the lymphocytes are "flower cells"

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

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

## Question #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 jirovecii
- On evaluation the lymphocyte count is 2,000 cells/µl; the CD4 count is 750 cells/µl and the hematology technician remarks that some of the lymphocytes are "flower cells"

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

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

## 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
- NOT a contraindication for transplantation
- No indication for ART

### Associated Infections

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

HTLV-II

- Not a cause of disease
- A distractor

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

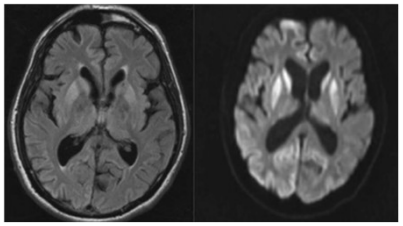
## Slow Viruses

## Question #9: Prion Diseases

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

### How was this illness most likely acquired?

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



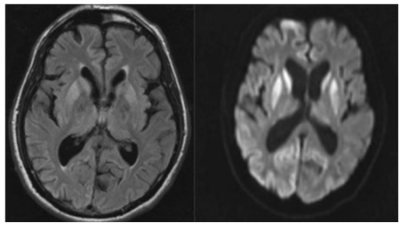
Flair Diffusion Weighted imaging

## Question #9: Prion Diseases

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

### How was this illness most likely acquired?

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



Flair Diffusion Weighted imaging

## Prion Diseases:
### Transmissible Spongiform Encephalopathies

- **Spontaneous (N=~6000 worldwide PER YEAR)**
  - Sporadic Creutzfeldt-Jakob disease (**sCJD**)
- **Hereditary (N ~600-900 PER YEAR worldwide)**
  - Autosomal Dominant
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)
- **Associated with specific exposure**
  - Ingestion of beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "**vCJD**" (**N = 228 TOTAL** cases, most recent case 2024)
      - Blood transfusion from individual with vCJD (4 cases)
  - Human brains
    - Kuru (**N= ~**2700 TOTAL cases; last known case reported 2009)
- **Associated with a medical procedure (N ~ 450 TOTAL cases)**
- Iatrogenic "iCJD"

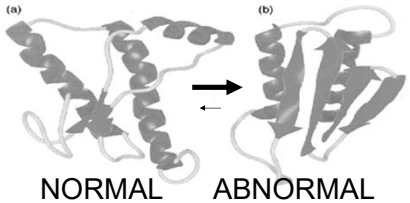
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.ucl.ac.uk/brain-sciences/prion/about-us/kuru


© 2026 Infectious Disease Board Review

## Prion Disease Pathogenesis
### A. Initiation

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




NORMAL ABNORMAL

Transition to abnormal conformation is rare but essentially irreversible

Naturally occurring mutations favor interconversion

## Prion Disease Pathogenesis
### B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation

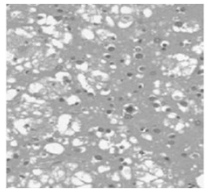


Prion Protein
Mutant Conformation

Direct contact



*Prion Protein*
*Mutant Conformation*



Disaggregase chaperone proteins may scavenge these proteins with mutant conformation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

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

## Dementia Comparison

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

## Question #10: Prion Diseases

- 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)

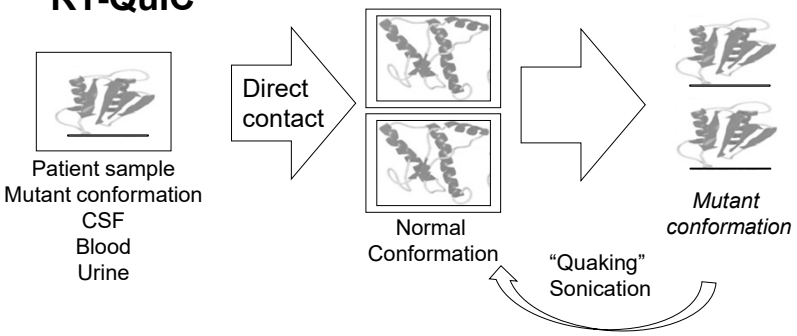
## Question #10: Prion Diseases

- 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)

## Abnormal Prion Detection
### RT-QuIC



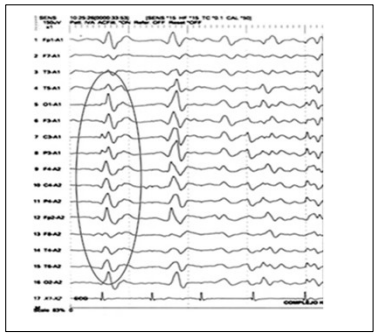

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Currently being adapted for diagnoses of other conformational diseases

**Spontaneous Creutzfeldt-Jacob Disease (sCJD)**

## Typical Clinical Presentation

- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves
- Rapid progression
- RT-QuIC elevated
- Supportive, not specific:
  - Elevated Tau
  - 14-3-3



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Herran, BMC Neurology 2018


© 2026 Infectious Disease Board Review

## Question #11: Prion Diseases

- A 44-year-old man presents with dementia progressing over the last 18 months
- He was born in rural Indonesia, lived in London and ate beef from 1985-2025, then moved to Philadelphia

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

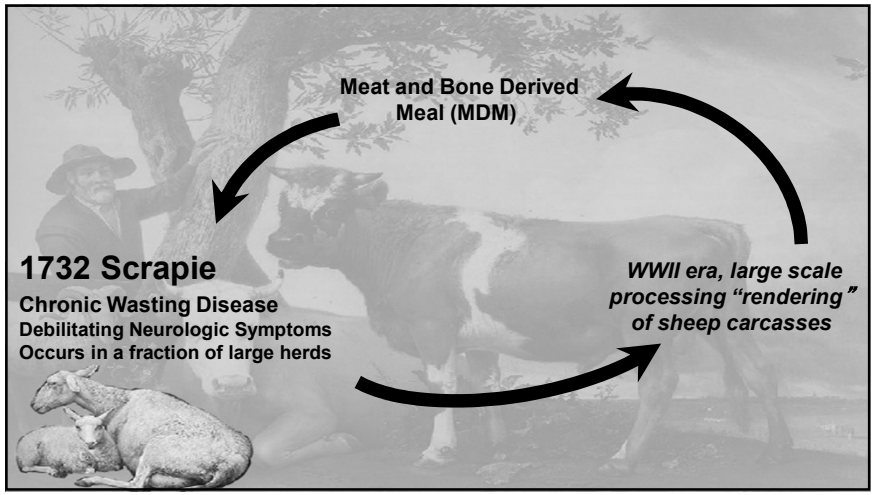
A. Kuru
B. Variant Creutzfeldt-Jacob Disease
C. Familial Creutzfeldt-Jacob Disease
D. Rabies

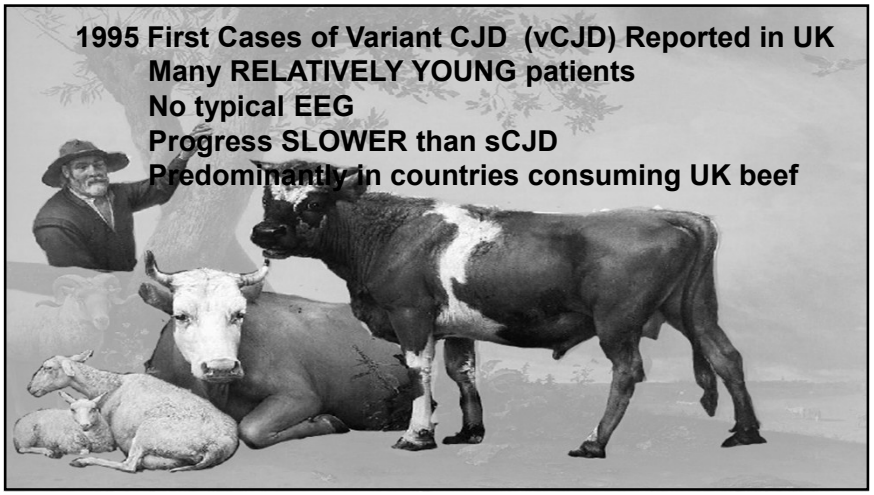
## Question #11: Prion Diseases

- A 44-year-old man presents with dementia progressing over the last 18 months
- He was born in rural Indonesia, lived in London and ate beef from 1985-2025, then moved to Philadelphia

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

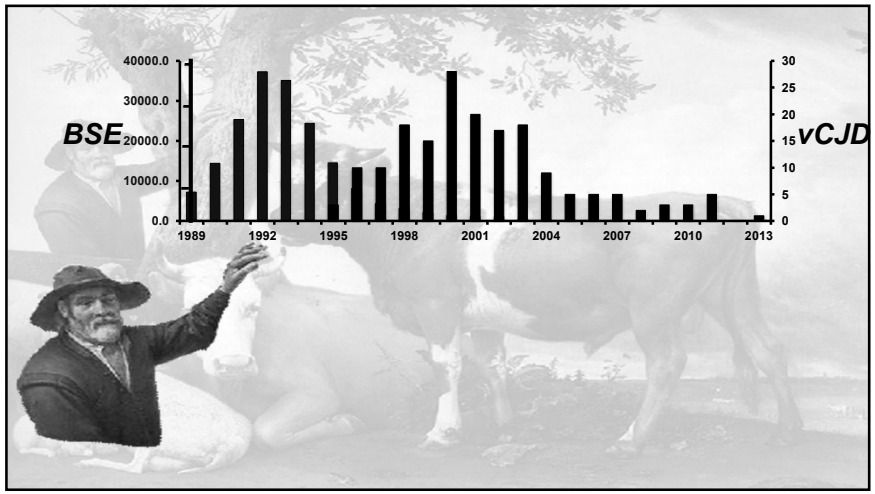
A. Kuru
**B. Variant Creutzfeldt-Jacob Disease***
C. Familial Creutzfeldt-Jacob Disease
D. Rabies





© 2026 Infectious Disease Board Review

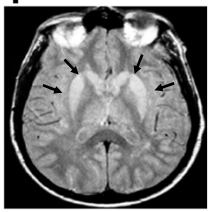



## Numbers of vCJD Cases Worldwide

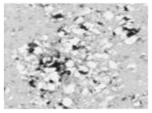
| | |
|---|---|
| United Kingdom | 177 |
| France | 26 |
| Spain | 5 |
| US | 4 |
| All acquired OUTSIDE of US | |
| Ireland | 4 |
| Netherlands, Italy | 3 |
| Portugal, Canada, Italy | 2 each |
| Saudi Arabia, Japan, Taiwan | 1 each |
| Single cases reported 2018, 2021 | |

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

## sCJD Sporadic CJD

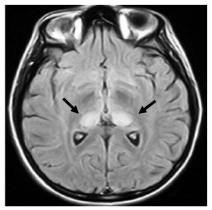


*T2 axial proton weighted*
*Putamen and caudate head*
*"Double hockey stick sign"*

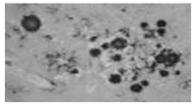


*"Abnormal Prion Accumulation"*

## vCJD Variant CJD



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



*"Florid Plaques"*

## Question #12: Prion Diseases

- A 40-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


© 2026 Infectious Disease Board Review

## Question #12: Prion Diseases

- A 40-year-old man recently emigrated from Japan presents with rapidly progressing dementia over the course of months
- He underwent a meningioma resection with dura mater graft in Japan 35 years ago
- He is an avid deer hunter and consumes venison

### What is the most likely cause of his dementia?

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

## Iatrogenic CJD ~450 cases

**Definite Causes**
- Pituitary extracts
  - Human Growth Hormone
  - Delay may be >40 y
- Dura mater grafts
  - Mostly Lyodura brand
  - Japan has highest number of cases
- Transplants (RARE)
  - Corneal
  - Pericardium
  - Liver
- Instrumentation/Laboratory Accident
  - Implanted EEG
  - Stereotactic procedures

**No Link**
- Vaccines
- Feces
- Saliva
- Sputum
- Bovine insulin
- Semen, vaginal secretions

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Summary

| | sCJD | Familial CJD | iCJD | vCJD |
|---|---|---|---|---|
| Source | Spontaneous event | Autosomal Dominant | Human growth hormone<br>Dura mater graft | Ingested beef |
| Distribution | Worldwide | Worldwide | Human growth hormone: US, Europe<br>Dura mater graft: Japan | Linked to Beef originating largely in UK. US cases all have travel history |
| Median Age of onset (y) | 68 | 40-60 | 51-58 | 26-28 |
| Approximate Survival | 8 months | up to 5 y | 15 months | 14 months |
| EEG | Periodic sharp waves | Variable | few data | No Periodic Sharp Waves |
| MRI (DWI) | "Double Hockey Stick" | Variable | Few Data, Double Hockey Stick | "Pulvinar sign" |
| Pathology | Abnormal Prion Protein deposits | Abnormal Prion Protein deposits | Abnormal Prion Protein deposits | "Florid Plaques" |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Prions Reference Material


© 2026 Infectious Disease Board Review

## CJD and Recommendations

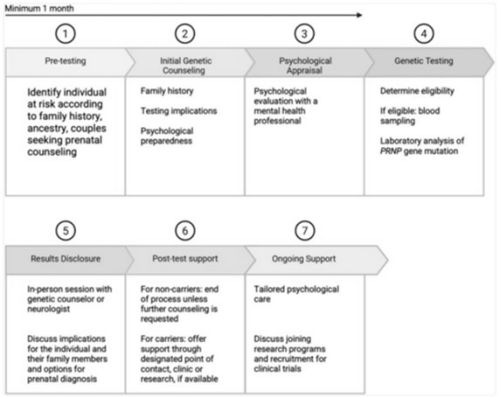
**Patient**

- 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

## CJD and Recommendations

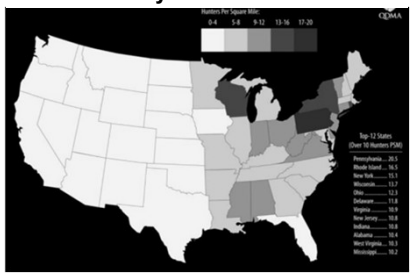



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

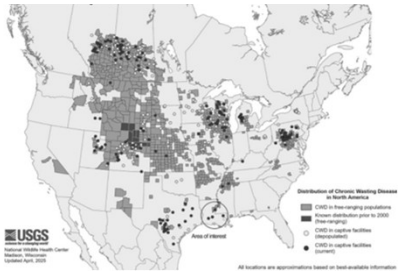
## Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

Geography (rural) or activity (hunting) are DISTRACTORS

**Hunter Density**



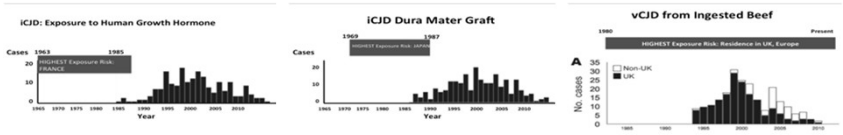
**Chronic Wasting Disease in Deer**




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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 |




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

## 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

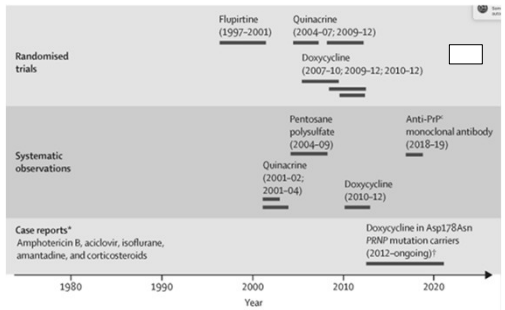
## CJD and Blood Supply

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

## *Transmissible Spongiform Encephalopathy*
### Infection Control Issues

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

## *Transmissible Spongiform Encephalopathy*
### Multiple Trials BUT NO FDA Approved Therapy




*Zerr, Lancet Neurology 2022*

**PRN100 Antibody Under Study**
- Anti-Prion antibody/G4 isotype
  - UK /J. Collinge/N=6
  - Achieved antibody levels in
  - CSF
  - No disease reversal
  - ?Stabilization of rating scales

Future: Disaggregase induction

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

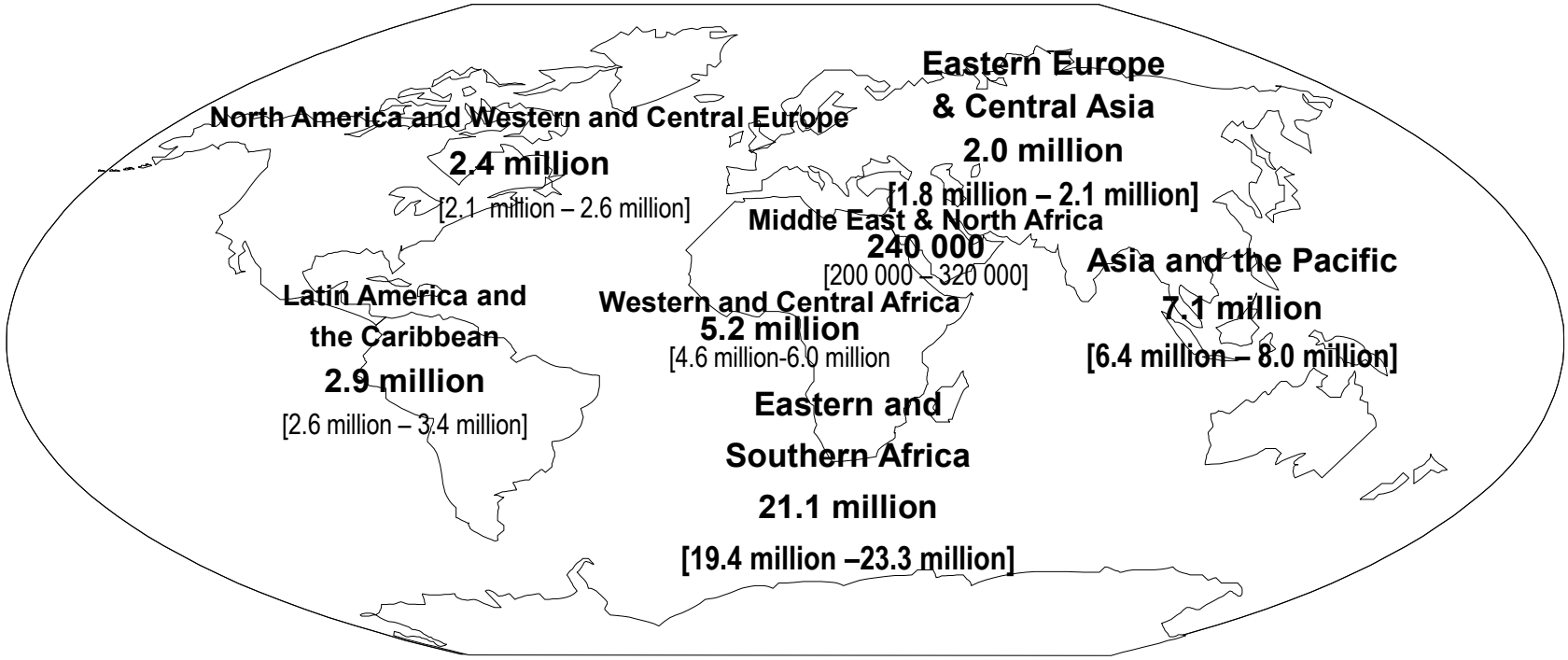
## Resources

- **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**


© 2026 Infectious Disease Board Review

# Estimated Numbers of Adults and Children with HIV 2025

## HIV prevalence: 40.9 million persons with HIV




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## >75% access to antiretroviral therapy

## HIV incidence: 1.2 million new infections/year

UNAIDS

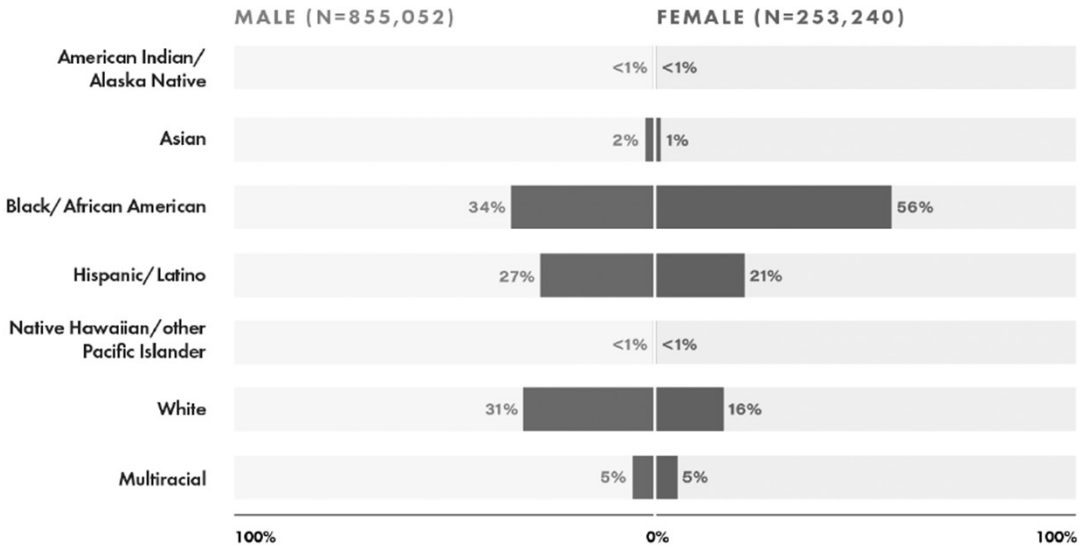
**32 Clinical Manifestations of Human Retroviral Diseases and Slow Viruses**

*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

# Current US Epidemic

## Prevalence: 1.1 Million




75% Male
70% Persons of Color

Diagnoses: 31,500 in 2023
**CDC, 2024**

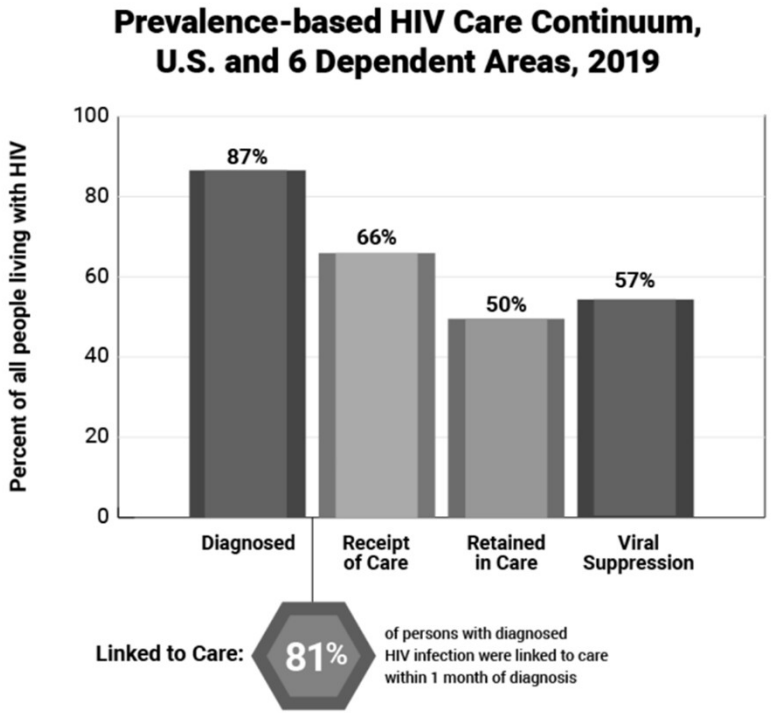
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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


© 2026 Infectious Disease Board Review

# 2030 US HIV Public Health Goals: Treatment Cascade

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




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

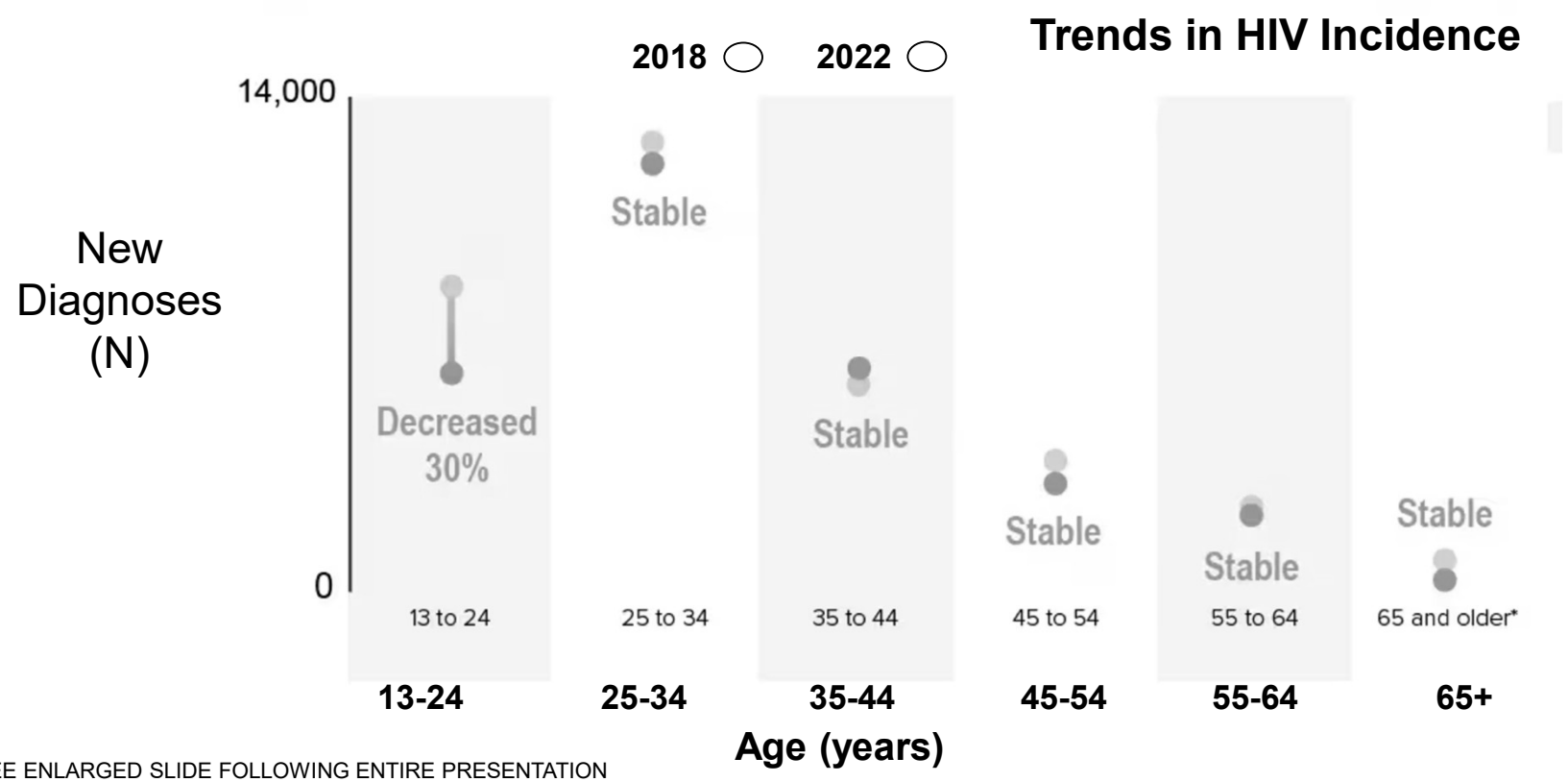
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

CDC


© 2026 Infectious Disease Board Review

# 2030 US HIV Public Health Goals: Transmission

**90% Reduction in Incidence by 2030**




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

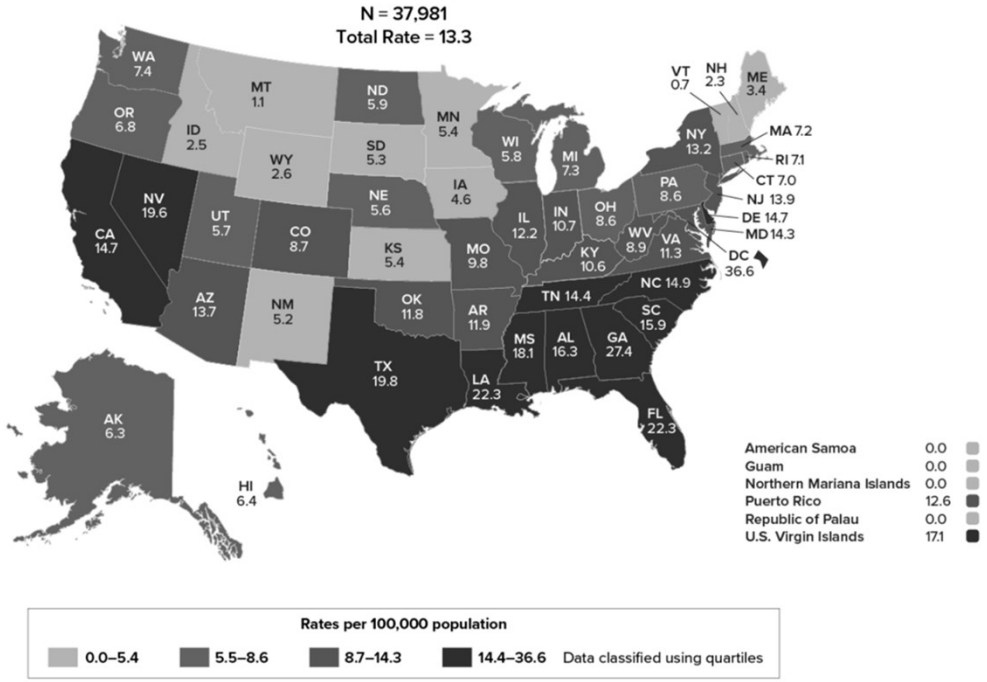
CDC



© 2026 Infectious Disease Board Review

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

43% all new Diagnoses are in Southeast

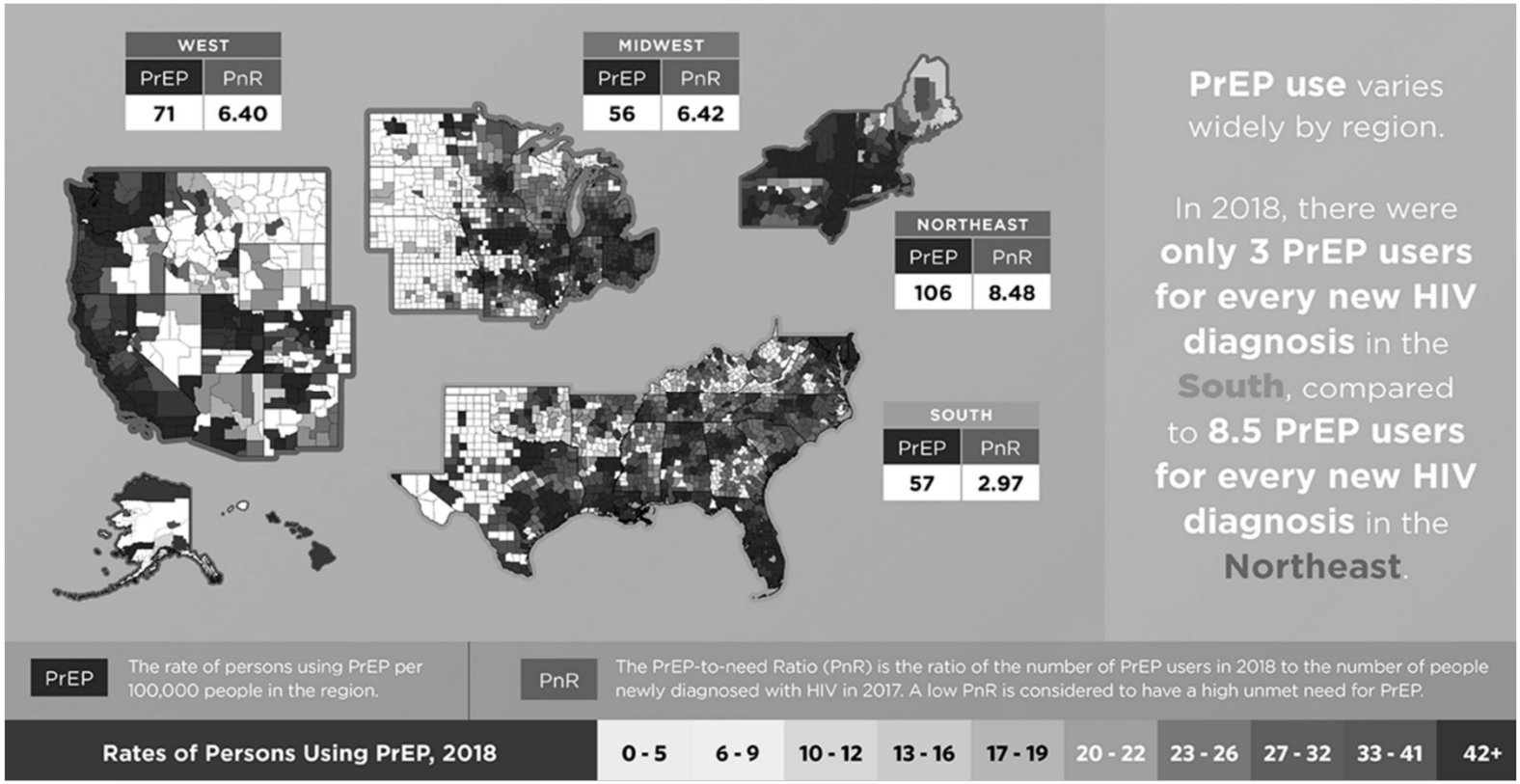



Note. 2019 Data. Estimates were derived from a CD4 depletion model using HIV surveillance data. Estimates rounded to the nearest 100 for estimates >1,000 and to the nearest 10 for estimates ≤1,000 to reflect model uncertainty.
†Total estimate for the United States does not include data for Puerto Rico.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

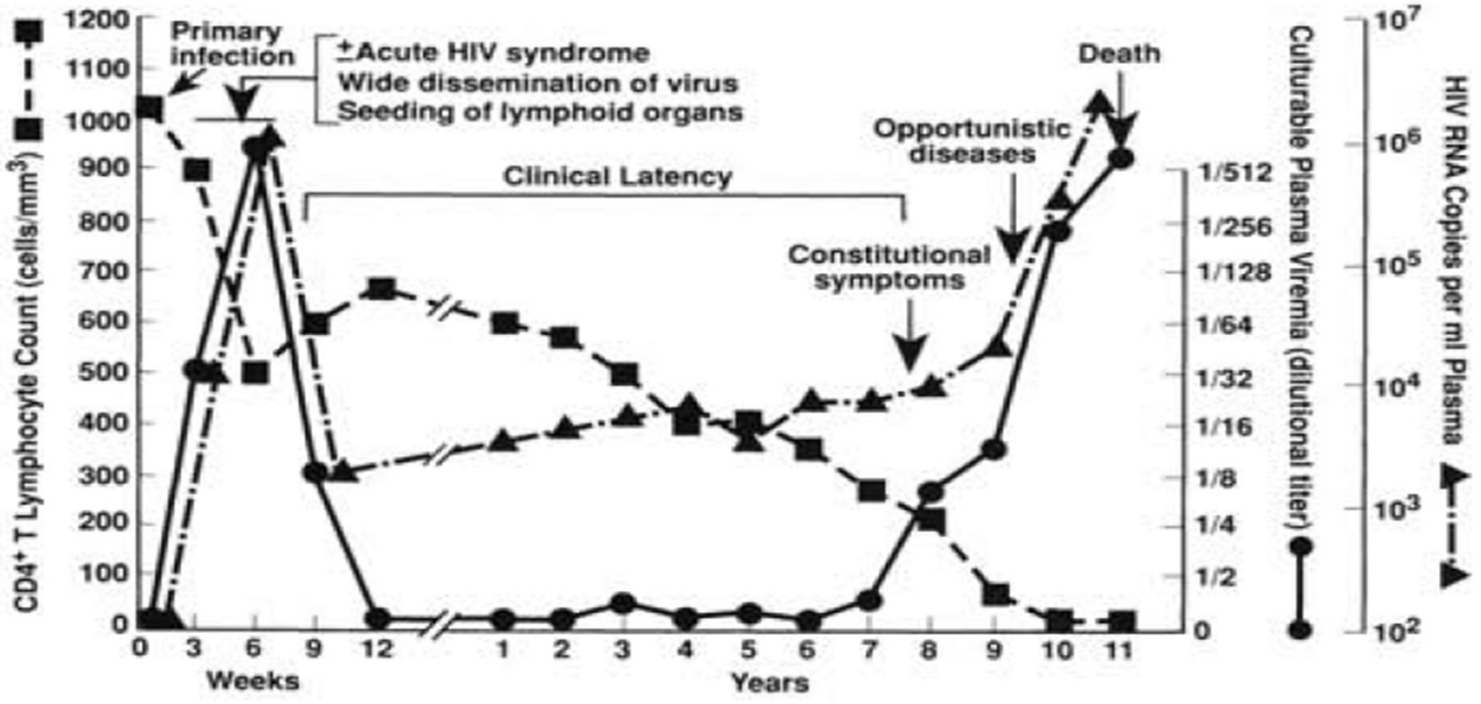
# PrEP-to-Need Ratio:
## PrEP using/HIV Diagnoses




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# HIV Infection Course




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Acute HIV Syndrome

| | Percent Reporting | | |
|---|---|---|---|
| Sign/Symptom | 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 too work | 1 | 44 | 58 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# HIV-1 and HIV-2

| Characteristic | HIV-2 | HIV-1 |
|---|---|---|
| **Epidemiology** | | |
| Geography | West/Central Africa | Worldwide |
| Local Distribution | Urban = Rural | Urban > Rural |
| Age-Specific Prevalence | Stable or Decreasing | Increasing |
| **Pathogenesis** | | |
| Average Age at Diagnosis | 45-55 | 20-34 |
| Maternal-Fetal (without RX) | 0-4% | 20-35% |
| Kaposi Sarcoma | Less Common (10X) | More Common |
| **Therapy** | | |
| | NRTI, PI, INSTI, Corec | All Antiretrovirals |
| | **NOT NNRTI, Fusion, (Capsid)** | |
| **Diagnosis** | | |
| Screening | HIV ½ ELISA | HIV ½ ELISA |
| Confirmatory | Supplemental (e.g., Geenius) | Supplemental (Qual HIV RNA) |
| **Monitoring** | | |
| | HIV-2 RNA Assay | HIV-1 RNA Assay |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 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
- NOT a contraindication for transplantation
- No indication for ART

## Associated Infections

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

HTLV-II

- Not a cause of disease
- A distractor

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Prion Diseases:
## Transmissible Spongiform Encephalopathies

- **Spontaneous (N=~6000 worldwide PER YEAR)**
  - Sporadic Creutzfeldt-Jakob disease (**sCJD**)
- **Hereditary (N ~600-900 PER YEAR worldwide)**
  - Autosomal Dominant
  - Familial (fCJD)
  - Gerstmann-Straussler-Sheinker (GSS)
  - Fatal Familial Insomnia (FFI)
  - Fatal Sporadic Insomnia (FSI)
- **Associated with specific exposure**
  - Ingestion of beef from cows with Bovine Spongiform Encephalopathy
    - Denoted "Variant CJD", "**vCJD**" (**N = 228 TOTAL** cases, most recent case 2024)
      - Blood transfusion from individual with vCJD (4 cases)
  - Human brains
    - Kuru (**N= ~**2700 TOTAL cases; last known case reported 2009)
- **Associated with a medical procedure (N ~ 450 TOTAL cases)**
- Iatrogenic "iCJD"

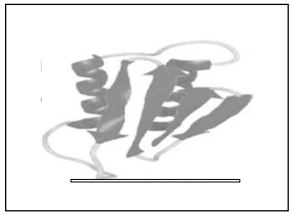
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.ucl.ac.uk/brain-sciences/prion/about-us/kuru


© 2026 Infectious Disease Board Review

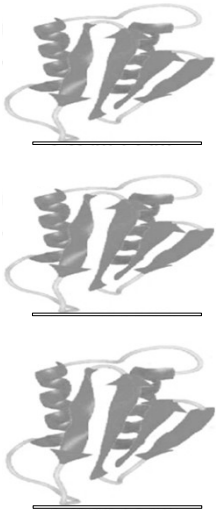
# Prion Disease Pathogenesis
## B. Propagation

Protein-Protein Contacts recruit normal proteins into abnormal conformation

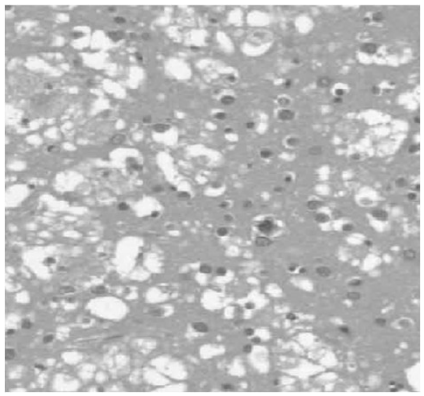


Prion Protein
Mutant Conformation

Direct contact



*Prion Protein*
*Mutant Conformation*



Disaggregase chaperone proteins may scavenge these proteins with mutant conformation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

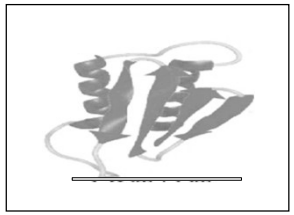
# Dementia Comparison

| 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

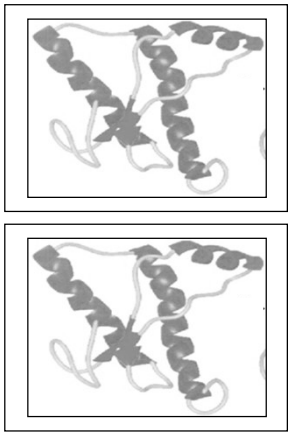

© 2026 Infectious Disease Board Review

# Abnormal Prion Detection
## RT-QuIC

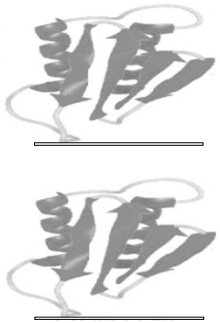


Patient sample
Mutant conformation
CSF
Blood
Urine

Direct contact



Normal Conformation



*Mutant conformation*

"Quaking" Sonication

Sensitivity 92% Specificity >99%

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

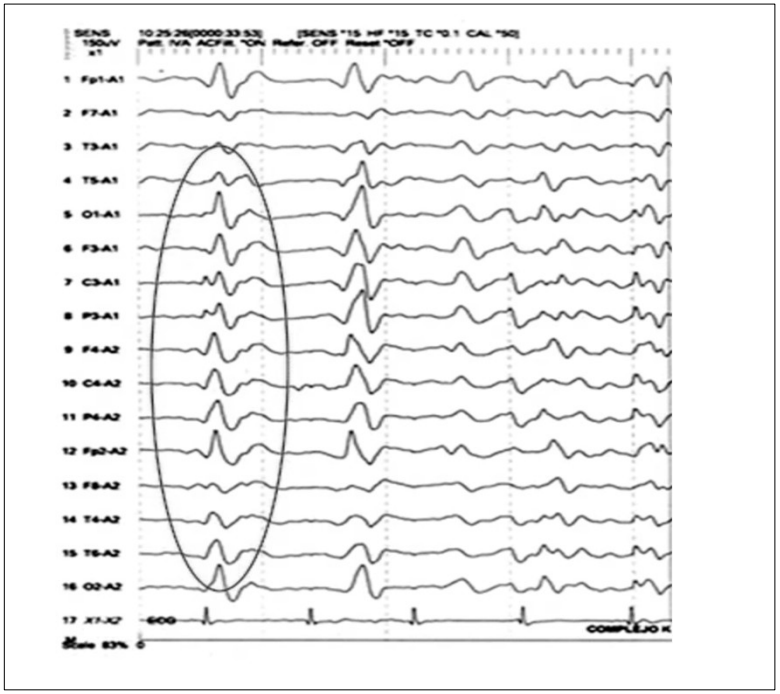
Currently being adapted for diagnoses of other conformational diseases


© 2026 Infectious Disease Board Review

## Spontaneous Creutzfeldt-Jacob Disease (sCJD)

# Typical Clinical Presentation

- Classic Clinical Triad
  - Dementia
  - Myoclonus
  - EEG: periodic sharp waves
- Rapid progression
- RT-QuIC elevated
- Supportive, not specific:
  - Elevated Tau
  - 14-3-3



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Herran, BMC Neurology 2018



© 2026 Infectious Disease Board Review

# Iatrogenic CJD ~450 cases

**Definite Causes**

- Pituitary extracts
  - Human Growth Hormone
  - Delay may be >40 y
- Dura mater grafts
  - Mostly Lyodura brand
  - Japan has highest number of cases
- Transplants (RARE)
  - Corneal
  - Pericardium
  - Liver
- Instrumentation/Laboratory Accident
  - Implanted EEG
  - Stereotactic procedures

**No Link**

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

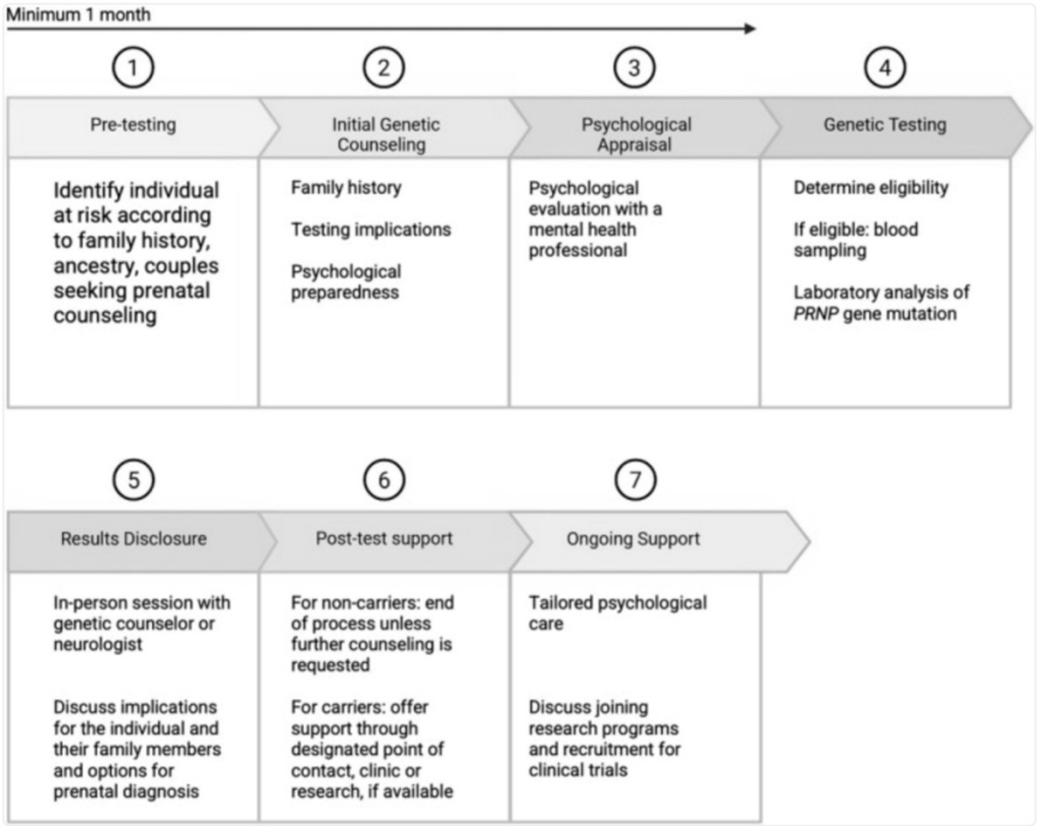
# Summary

| | sCJD | Familial CJD | iCJD | vCJD |
|---|---|---|---|---|
| Source | Spontaneous event | Autosomal Dominant | Human growth hormone<br>Dura mater graft | Ingested beef |
| Distribution | Worldwide | Worldwide | Human growth hormone: US, Europe<br>Dura mater graft: Japan | Linked to Beef originating largely in UK. US cases all have travel history |
| Median Age of onset (y) | 68 | 40-60 | 51-58 | 26-28 |
| Approximate Survival | 8 months | up to 5 y | 15 months | 14 months |
| EEG | Periodic sharp waves | Variable | few data | No Periodic Sharp Waves |
| MRI (DWI) | “Double Hockey Stick” | Variable | Few Data, Double Hockey Stick | “Pulvinar sign” |
| Pathology | Abnormal Prion Protein deposits | Abnormal Prion Protein deposits | Abnormal Prion Protein deposits | “Florid Plaques” |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# CJD and Recommendations



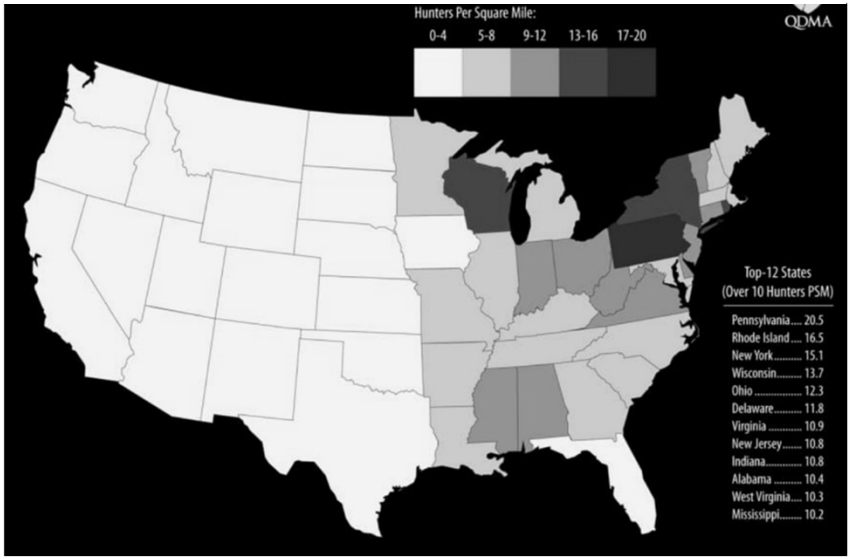

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

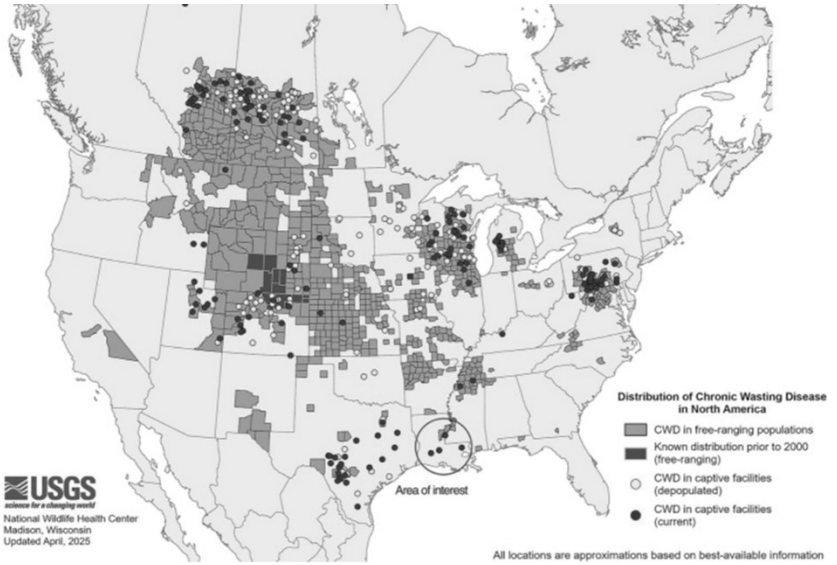
# Spontaneous Creutzfeldt-Jacob Disease (sCJD) Epidemiology

Geography (rural) or activity (hunting) are DISTRACTORS

## Hunter Density




## Chronic Wasting Disease in Deer

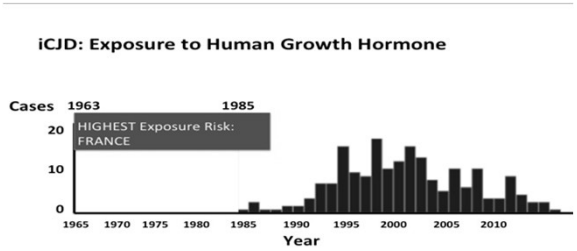


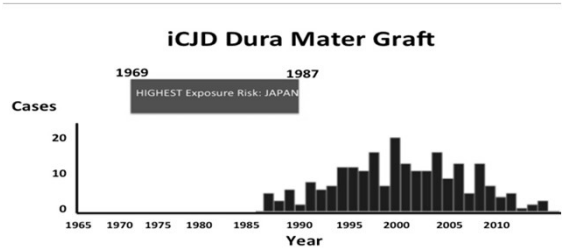

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

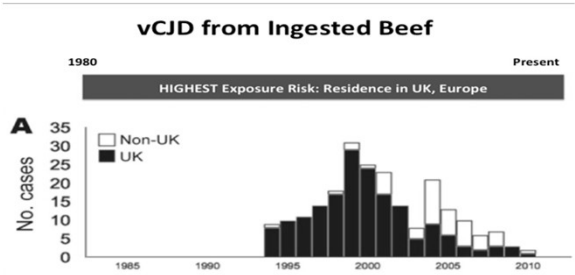

© 2026 Infectious Disease Board Review

# 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 |



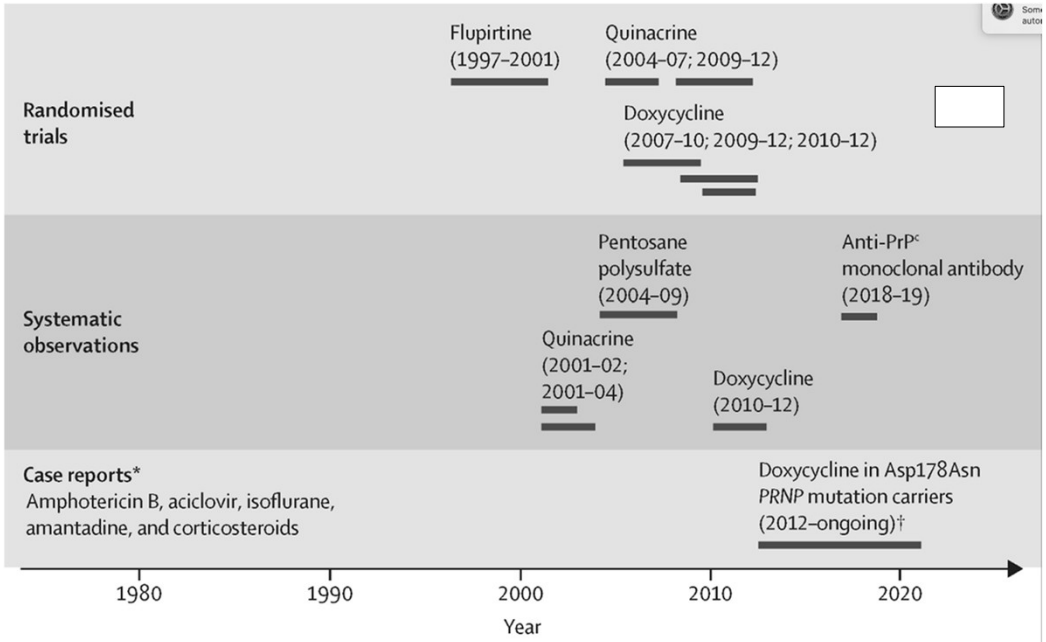




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# *Transmissible Spongiform Encephalopathy*
## Multiple Trials BUT NO FDA Approved Therapy




*Zerr, Lancet Neurology 2022*

**PRN100 Antibody Under Study**

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

Future: Disaggregase induction

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**33**

# HIV-Associated Opportunistic Infections I

**Henry Masur, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

**Tuesday, August 25, 2026**

---

**34**

# HIV Diagnosis

**Frank Maldarelli, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# HIV Diagnosis

**Frank Maldarelli, MD/PhD**
**Bethesda, MD**

07/20/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Question #1

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

### 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

## 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***

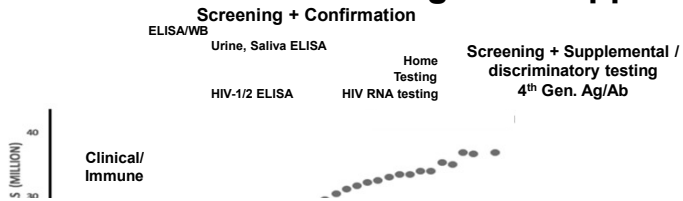


© 2026 Infectious Disease Board Review

# HIV Diagnosis:
**New Modalities and New Terminology Old Limitations Persist**

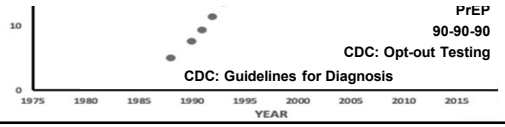
- HIV Diagnosis
  - History
  - Physical
  - Laboratory testing
- Two-Step Diagnostic Approach
- No Laboratory Test is Perfect
- False positive results require resolution
- PrEP places new stress on testing performance

# Evolution of the HIV Diagnostic Approach




Diagnostics and Guidelines Lagged BEHIND the Epidemic

But are AHEAD of the Eradication




# 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

# Question #2

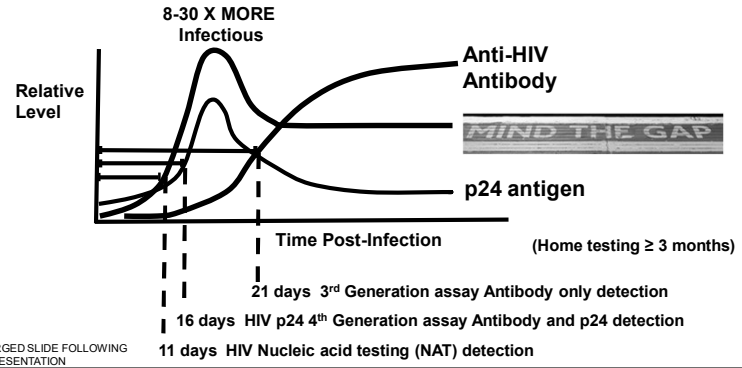
- 27-year-old female commercial sex worker working in Washington DC visits your clinic and requests PrEP
- She shows you her home HIV test, which she took yesterday, and which is non-reactive
- She has normal laboratory results and a negative pregnancy test

**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


*Speaker: Frank Maldarelli, MD*
© 2026 Infectious Disease Board Review

## HIV Detection: There is Always a Window Period




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

CDC 2014

## Detecting HIV Infection TWO STEPS

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

## Diagnosis of Early HIV Infection

**History, Physical, Laboratory Testing**

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

## Evaluation for HIV Infection During PrEP

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



© 2026 Infectious Disease Board Review

## Question #3

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

### 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

## Question #3

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

### 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

## 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

## Question #4

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

### Which of the following is most likely?

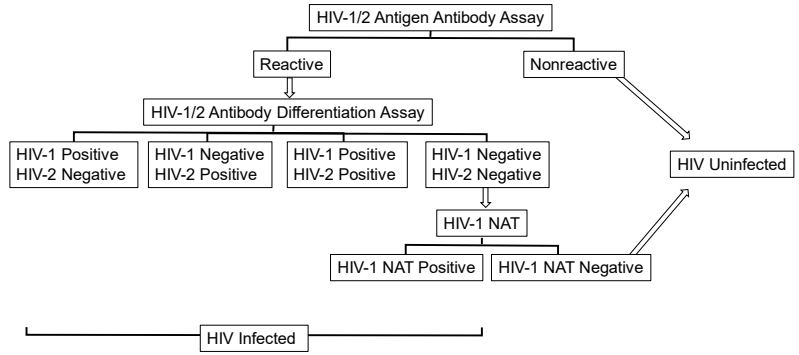
A. The patient is in the window period of HIV-1 infection
B. The patient is chronically infected with HIV-1 and has a viral load too low to be detected because he is a long term non progressor
C. The patient is not infected with HIV-1 or -2, all tests are false positive
D. The patient is infected with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


© 2026 Infectious Disease Board Review

## HIV-1 Long Term Non-Progressors

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

## HIV Diagnostic Algorithm




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Question #5

- 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

## Question #5

- 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


© 2026 Infectious Disease Board Review

# 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
- Autoimmune hemolytic anemia
- Angioblastic T cell lymphoma
- Hodgkin lymphoma

**Rheumatologic Diseases**
- Lupus
- Sjorgen
- Rheumatoid

**Iatrogenic**
- Vaccines
- Rabies
- T-dap
- Hepatitis B
- SARS-CoV-2
- HIV vaccine trials
- Lentiviral therapy (e.g., CAR-T)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# HIV Testing

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

# Pearls for Board Exam

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

Resources:

https://www.cdc.gov/hiv/guidelines/testing.html

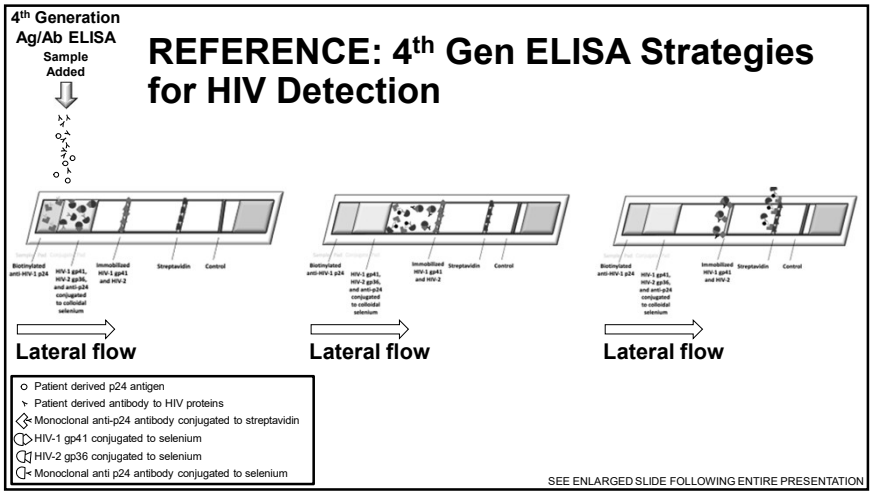
Fmaldarelli3@gmail.com

Reference slides follow

**No Test is Perfect**
- 4th Gen less sensitive
  - Acute
  - PEP/PrEP
  - Early Antiretroviral therapy
- False Positives
  - Pregnancy
- Mind the gap
  - Long gap for Home testing

**Board exam isn't perfect either…so don't overthink it**

# REFERENCE: 4th Gen ELISA Strategies for HIV Detection

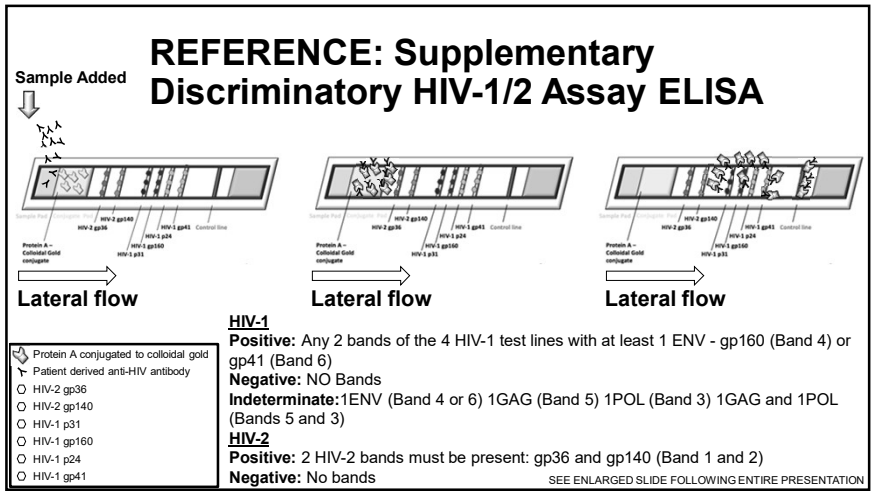


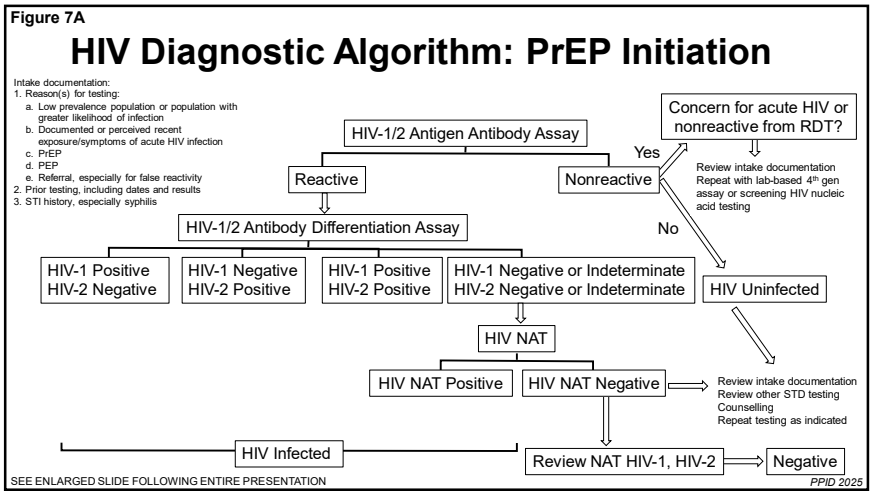

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

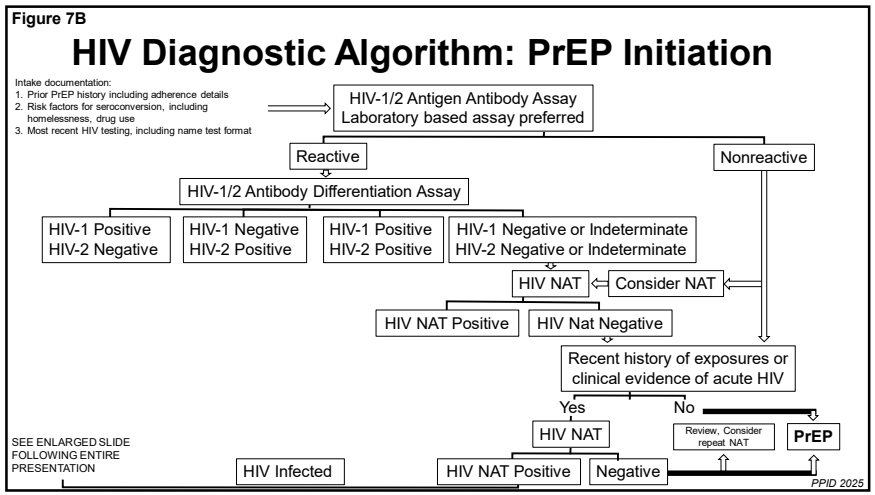


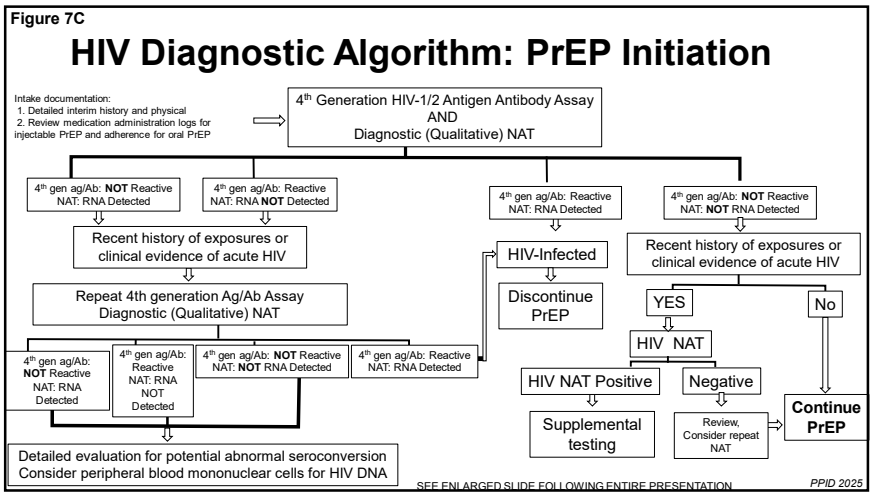
*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review



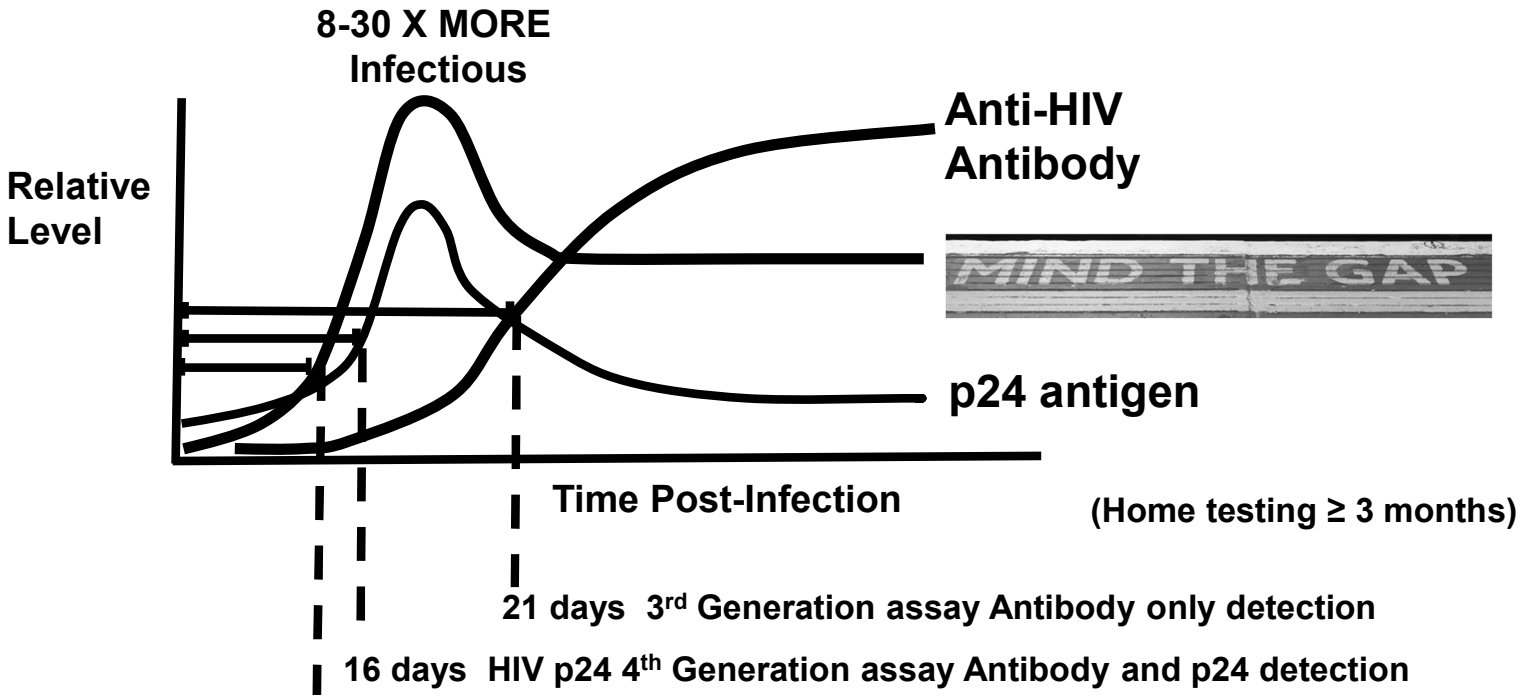





© 2026 Infectious Disease Board Review

# HIV Detection: There is Always a Window Period




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

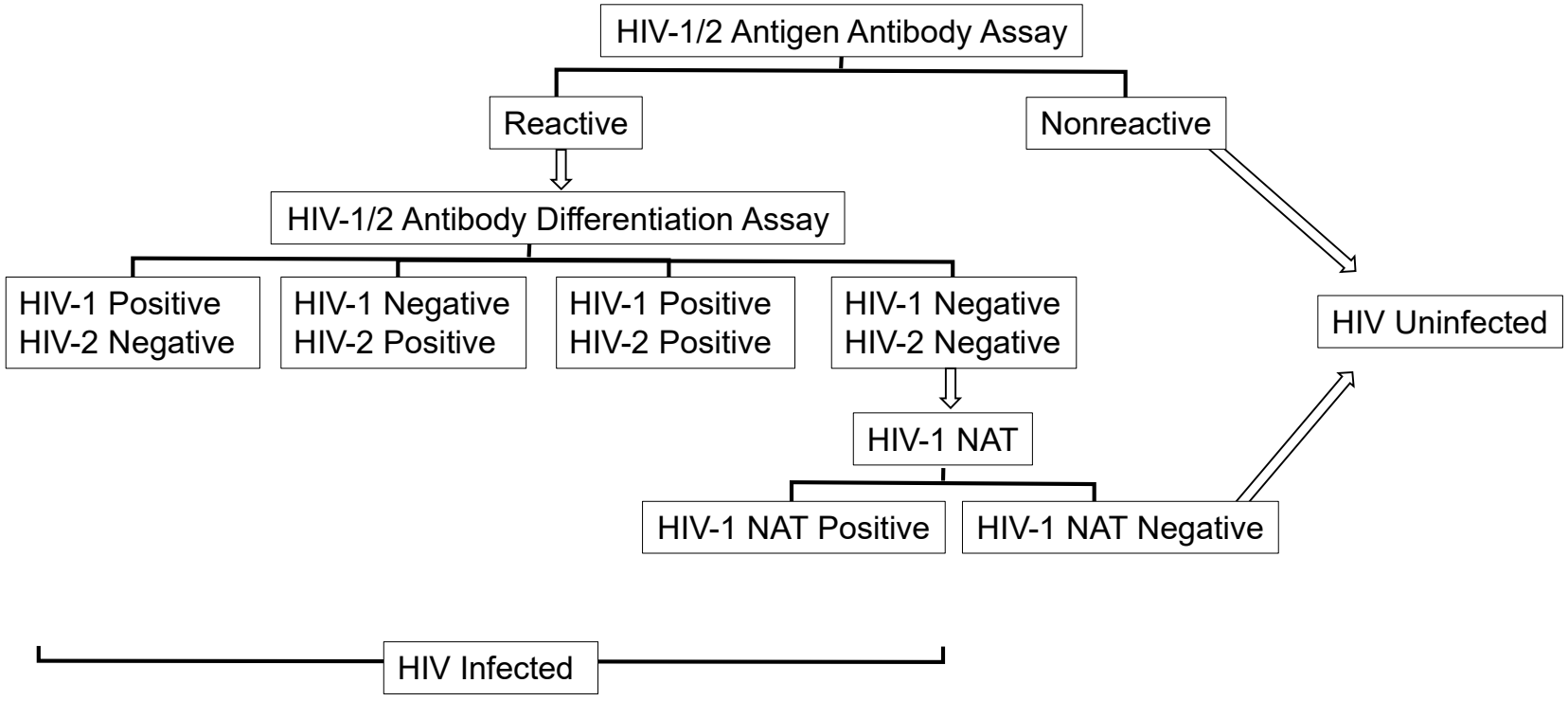
CDC 2014



*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

# HIV Diagnostic Algorithm




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 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
- Autoimmune hemolytic anemia
- Angioblastic T cell lymphoma
- Hodgkin lymphoma

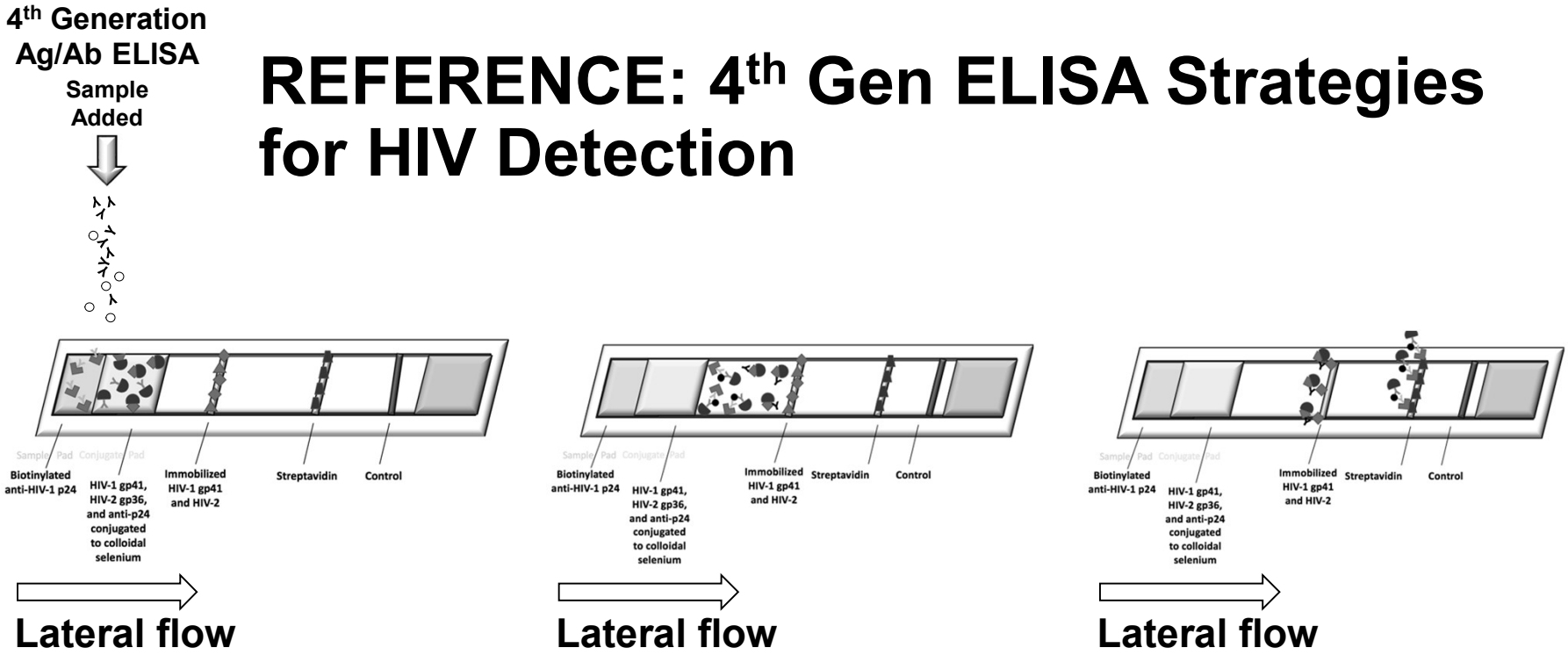
**Rheumatologic Diseases**
- Lupus
- Sjorgen
- Rheumatoid

**Iatrogenic**
- Vaccines
- Rabies
- T-dap
- Hepatitis B
- SARS-CoV-2
- HIV vaccine trials
- Lentiviral therapy (e.g., CAR-T)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# REFERENCE: 4th Gen ELISA Strategies for HIV Detection



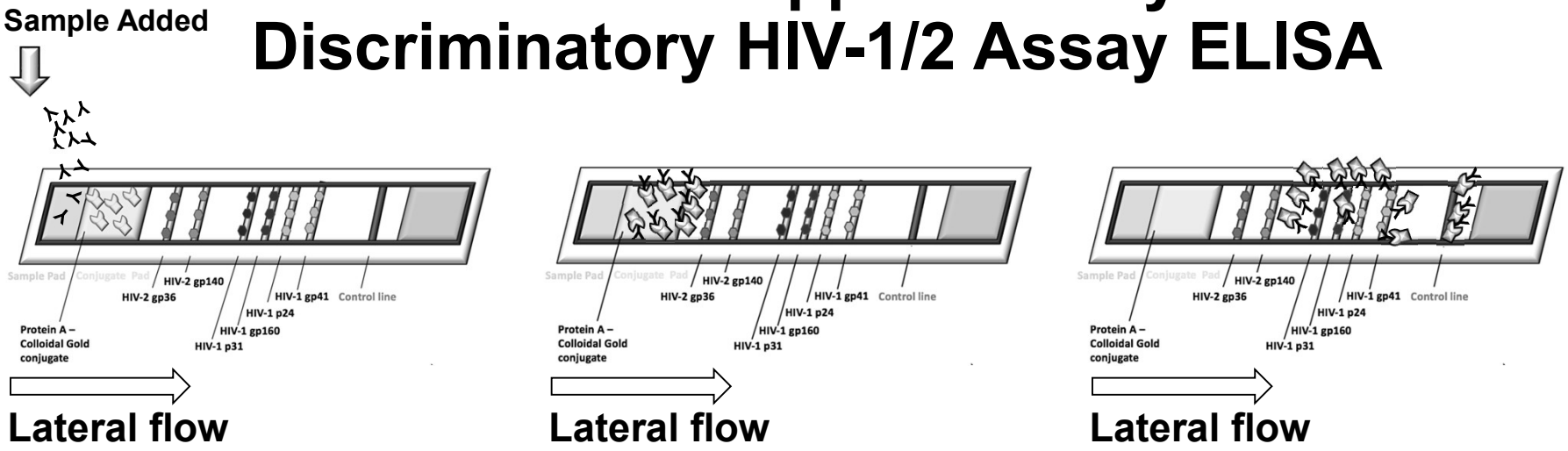

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

# REFERENCE: Supplementary Discriminatory HIV-1/2 Assay ELISA




- Protein A conjugated to colloidal gold
- Patient derived anti-HIV antibody
- HIV-2 gp36
- HIV-2 gp140
- HIV-1 p31
- HIV-1 gp160
- HIV-1 p24
- HIV-1 gp41

**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

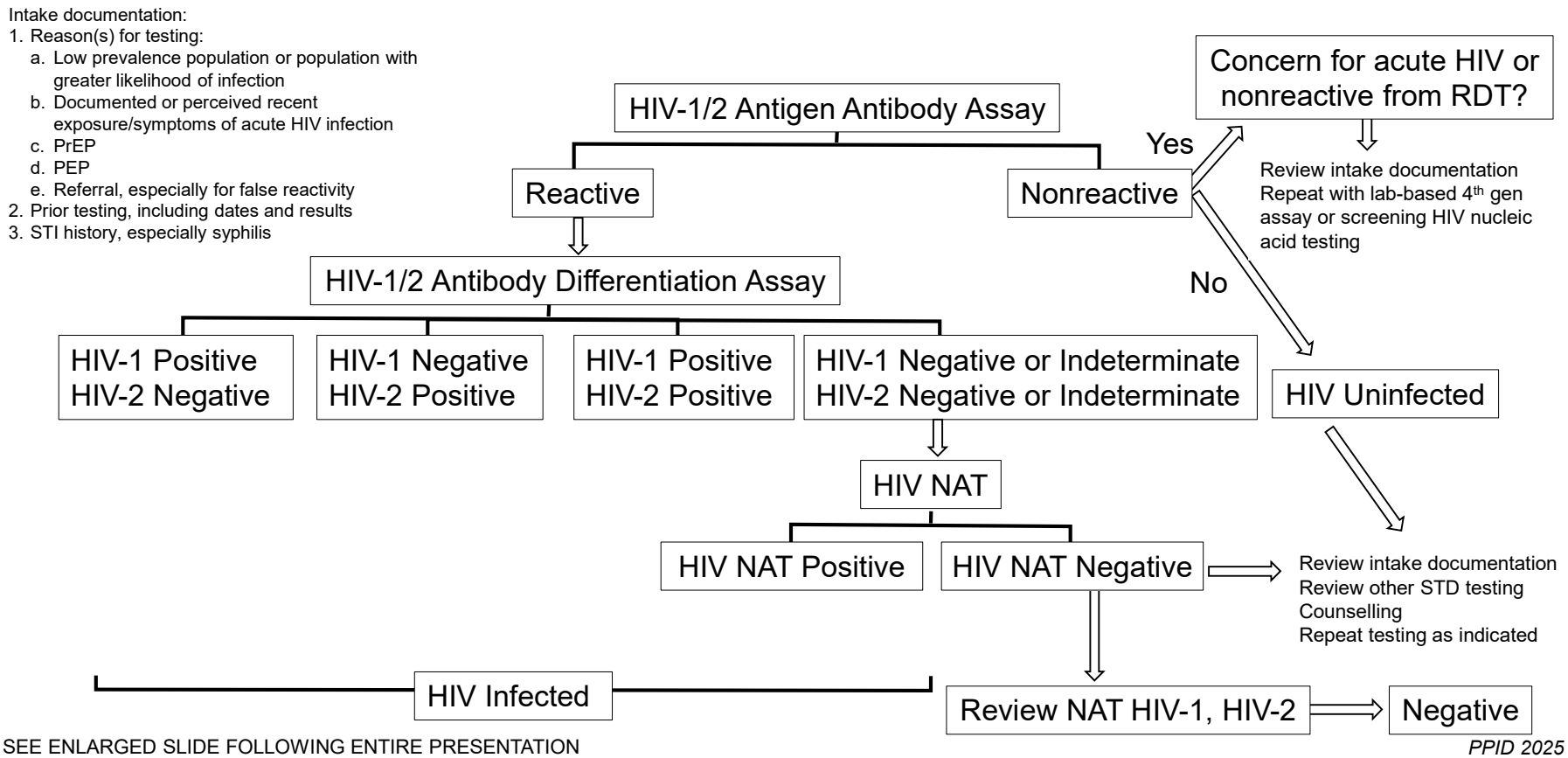
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

**Figure 7A**

# HIV Diagnostic Algorithm: PrEP Initiation




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

*PPID 2025*

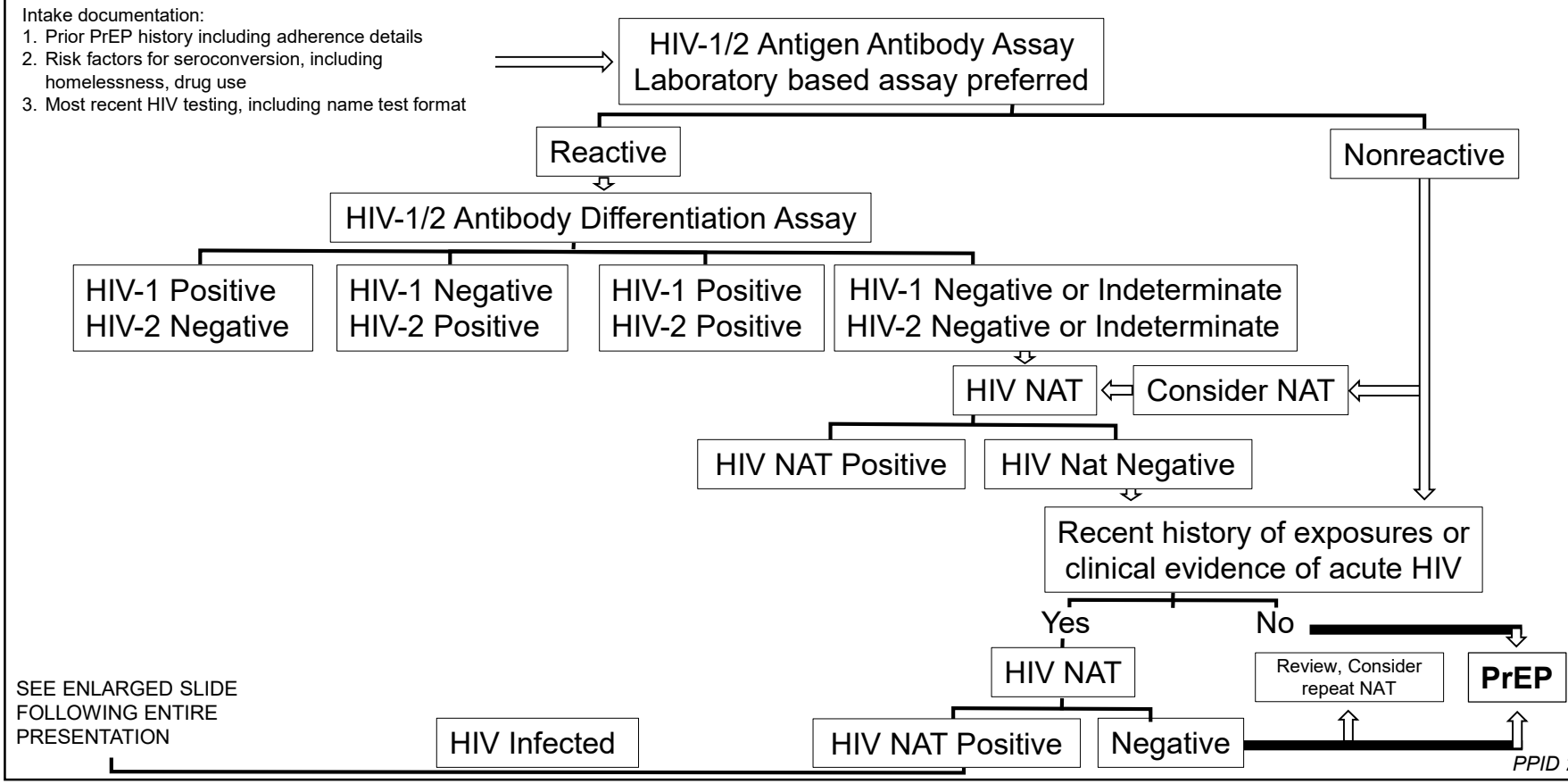


*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

**Figure 7B**

# HIV Diagnostic Algorithm: PrEP Initiation



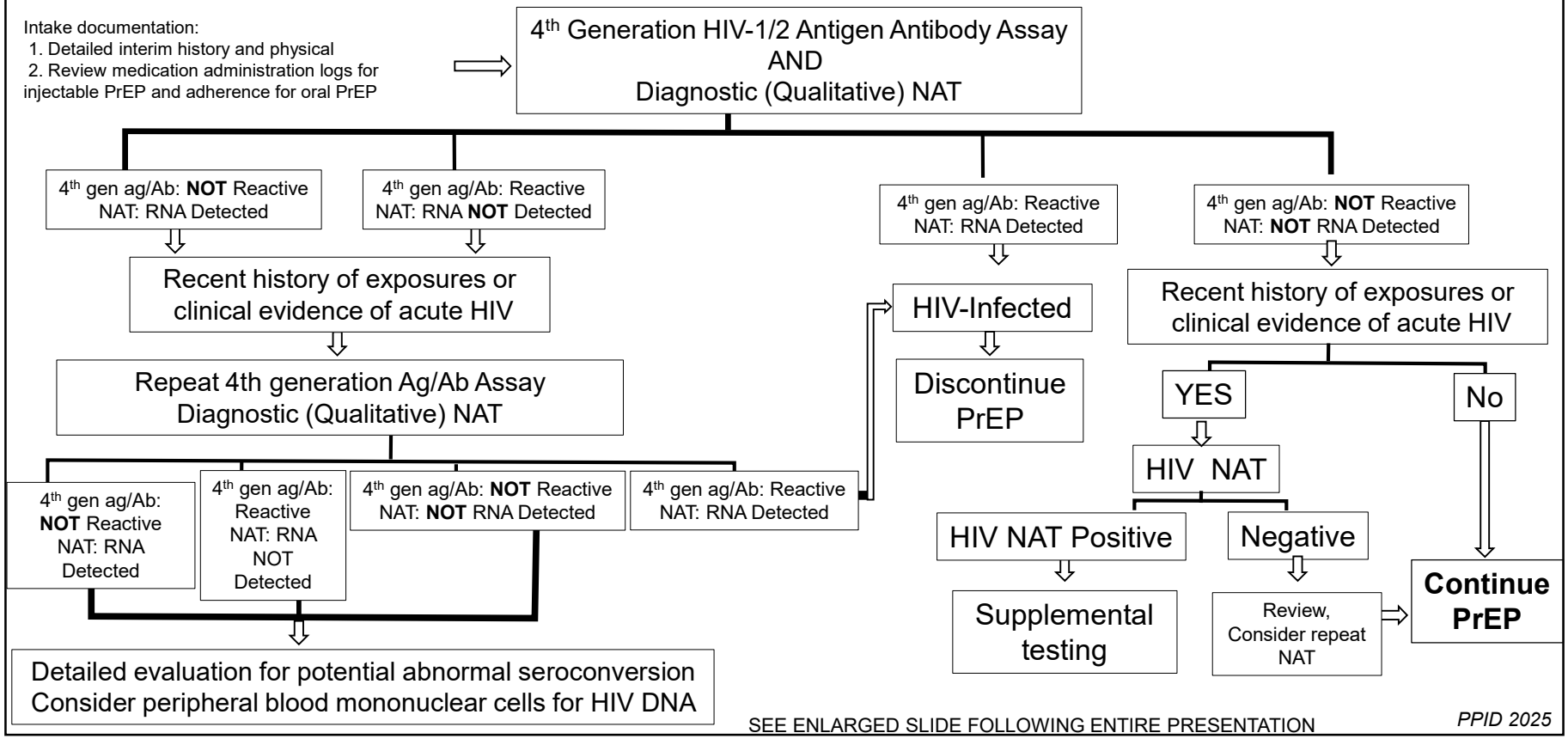

**34 HIV Diagnosis**

*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

**Figure 7C**

# HIV Diagnostic Algorithm: PrEP Initiation




**34 HIV Diagnosis**

*Speaker: Frank Maldarelli, MD*

© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**35**

# Antiretroviral Therapy

**Roy Gulick, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Antiretroviral Therapy (ART)

**Roy Gulick, MD**
**Weill Cornell Medicine**

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## ID Boards - Medical Content: 15% HIV

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## Antiretroviral Therapy (ART)

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

## When to Start?

## Question #1

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

### Do you recommend starting ART?

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

## Question #1

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

### Do you recommend starting ART?

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


© 2026 Infectious Disease Board Review

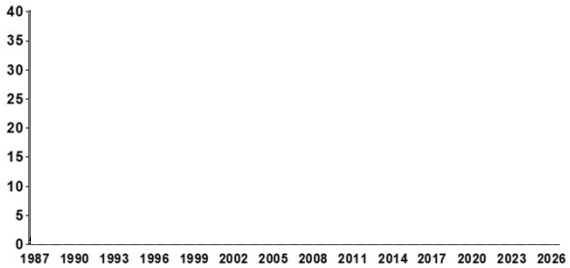
## When to Start?: Chronic Infection

| | AIDS/ symptoms | Asymptomatic | | | |
|---|---|---|---|---|---|
| | | CD4 <200 | CD4 200-350 | CD4 350-500 | CD4 >500 |
| **US DHHS 2026** www.clinicalinfo.hiv.gov | Recommended | | | | |
| **IAS-USA 2024** Gandhi JAMA 2025;333:609-628 | Recommended | | | | |

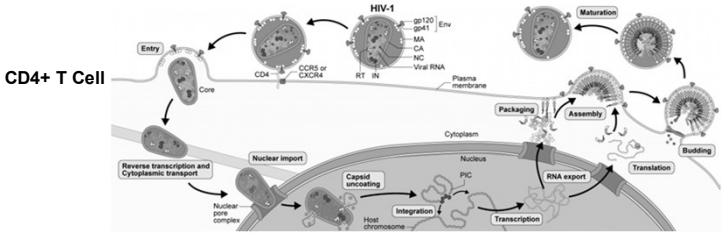
## Goal of Antiretroviral Therapy

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

## Antiretroviral Drug Approval: 1987 - 2026




## Life Cycle of HIV

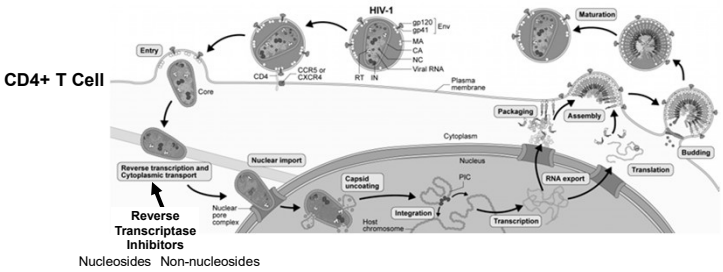



https://scienceofhiv.org/wp/animations/



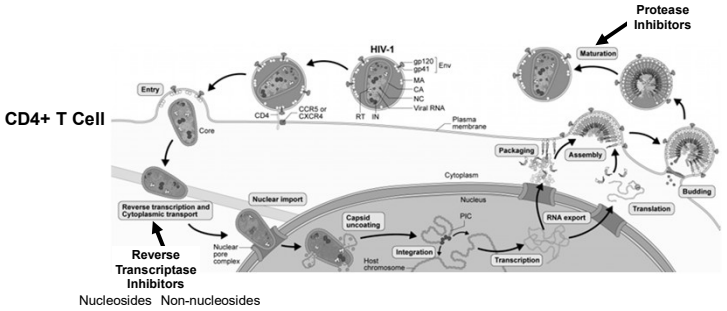
© 2026 Infectious Disease Board Review

## Life Cycle of HIV



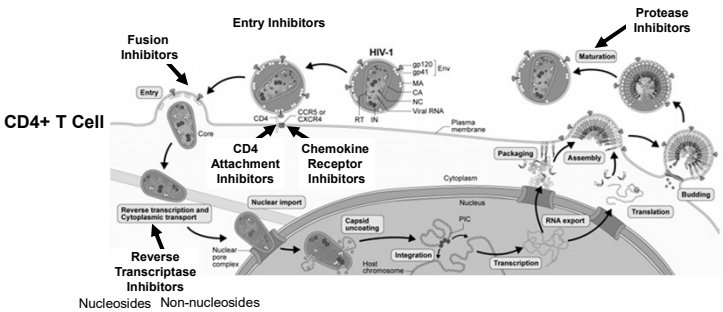

https://scienceofhiv.org/wp/animations/

## Life Cycle of HIV



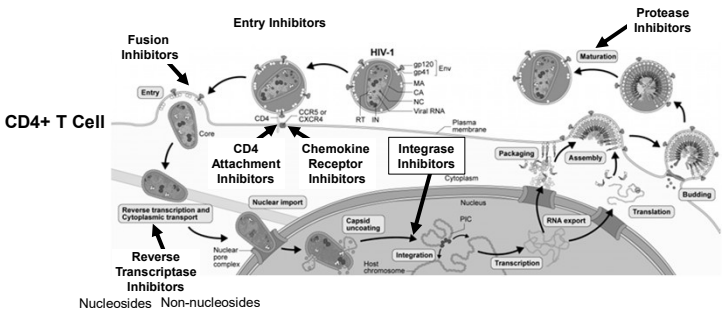

https://scienceofhiv.org/wp/animations/

## Life Cycle of HIV




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

## Life Cycle of HIV

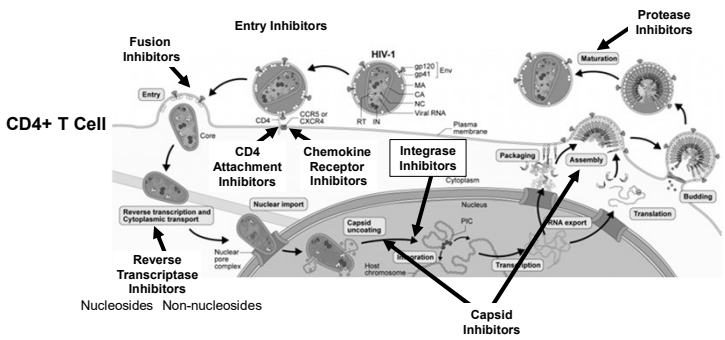



https://scienceofhiv.org/wp/animations/



© 2026 Infectious Disease Board Review

## Life Cycle of HIV




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

## Approved ART: 2026*

**Nucleoside/tide RTIs (NRTIs)**
- Zidovudine (ZDV, AZT)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Islatravir (ISL)
- 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, SQV, IDV, APV, FPV, + ENF (T-20) discontinued

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## What to Start?

## 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



© 2026 Infectious Disease Board Review

## 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***

## First ART Regimen: Individual Factors

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

## Recommended Regimens (For Most People) (1-2 NRTI + Integrase Inhibitor)

- **Integrase Inhibitor-based**
  - **Bictegravir**/tenofovir alafenamide (TAF)/emtricitabine (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)



## 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





© 2026 Infectious Disease Board Review

## 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 9/25/25 clinicalinfo.hiv.gov

## Choice of NRTIs

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25

## Choice of NNRTIs

| Drug | DHHS GL | Dose | Toxicities | Considerations |
|---|---|---|---|---|
| **Doravirine** (DOR) | Alternative | qd | ↓ CNS toxicity than EFV; ↓ lipids | TDF/FTC/DOR (1 pill, once-daily) |
| **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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25

## 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

## Choice of Integrase Inhibitors

| Drug | DHHS GL | Dosing | Toxicities | Considerations |
|---|---|---|---|---|
| **Bictegravir** (BIC) | Recommended with TAF/FTC | 1 coform-ulated pill | Few, ↑creat, wt gain | TAF/FTC/BIC (1 pill, qd); ↑ barrier to resistance |
| **Dolutegravir** (DTG) | Recommended with (TAF or TDF)/(FTC or 3TC); alternative with ABC/3TC | 50 mg qd (bid with II resistance) | Few, ↑creat, CNS, wt gain | ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance |
| **Cabotegravir** (CAB) | Recommended for Δ with viro suppression | IM with IM RPV | Few | All injectable regimen |
| **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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25

## Selected Drug Interactions 1

- **Integrase inhibitors**
  - Divalent cations (aluminum, calcium, iron, magnesium)
    - Bind to integrase inhibitors – separate or give with full meal
  - Metformin
    - Levels raised by bictegravir or dolutegravir
    - Titrate metformin dose
  - Rifampin
    - Need to double dose dolutegravir (or raltegravir)
    - Bictegravir dosing controversial

## Selected Drug Interactions 2

- Cytochrome P450 3A4 effects
- Most NNRTI (EFV, ETR, NVP – NOT DOR) are inducers
  - In general, ↓ levels of other metabolized drugs
- All 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: rifamycins, ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines, St. John's Wort, some HCV drugs

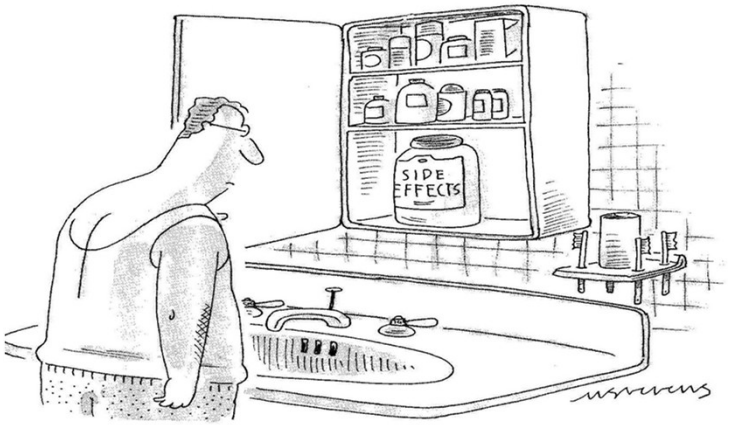
## ART: What NOT to Use as Initial therapy

- Monotherapy
- Nucleosides (NRTI)
  - 3 or 4 all-NRTI combination regimens
  - Older drugs (e.g. zidovudine)
- 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 (or ISL/DOR)

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review




## 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 but used
    - Dolutegravir during conception/very early pregnancy
      → Neural tube defects – RARE, not significantly ↑ vs. Other ART

## ART Side Effects 2

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

## 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)


© 2026 Infectious Disease Board Review

## When to Change?

## ART Change

- **Reasons:** adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, simplification
- Fundamental principle: maintain virologic suppression
- Review ART history, prior ART-associated toxicities, cumulative drug resistance testing results
- Within-class or between-class Δ usually works if no resistance
- Specific regimens:
  - DTG/3TC; DTG/RPV; DRV/r or /c + [3TC or FTC] or DTG; IM CAB + RPV; ISL/DOR
- Consideration: concomitant HBV infection

Based on DHHS Guidelines 9/25/25

## Why Does Treatment Fail Patients?

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

## Question #3

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


© 2026 Infectious Disease Board Review

## 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

## 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 9/25/25

## What to Change To?

## What To Change To?
### U.S. DHHS Guidelines

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

Based on DHHS Guidelines 9/25/25


© 2026 Infectious Disease Board Review

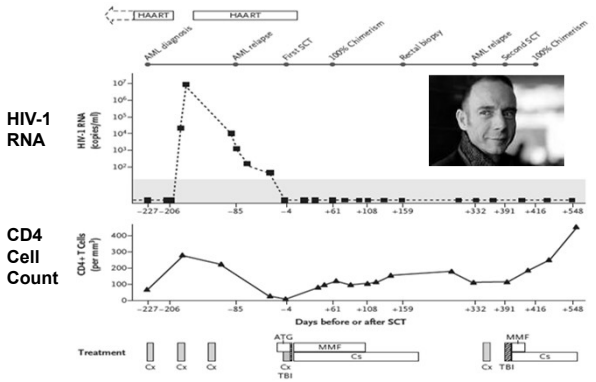
## Treatment = Prevention

## Treatment = Prevention

- Pregnant women with HIV Fowler NEJM 2016;375:1726
  - 3-drug ART ↓ transmission risk to child to 0.5%
- Men and women with HIV Cohen NEJM 2016;375:830
  Suppressive ART ↓ transmission to sexual partners by >93%
- HIV- post-exposure prophylaxis **(PEP)** Tanner CDC Guidelines MMWR 2025;74:1
  - 3-drug integrase inhibitor-based ART recommended for 4 weeks (e.g., TAF/FTC/BIC or TDF/FTC + DTG)
- At-risk men and women without HIV **(PrEP)** Molina NEJM 2015; McCormack Lancet 2016, Landovitz NEJM 2021; Delany-Moretlwe Lancet 2022; Bekker NEJM 2024; Kelley NEJM 2025; Choopanya Lancet 2013
  - ↓ HIV acquisition by sex >75-100% (TDF/FTC; TAF/FTC; IM CAB; SQ LEN)
  - ↓ HIV acquisition by injection drug use ~50% (TDF/FTC)

## Cure

## HIV Cure (N=~~1~~) 10+!




Hutter NEJM 2009;360:692

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**Cure #2** *first Latino
London
Gupta, Nature 2019;568:244
**Cure #3** *first woman
NYC
Hsu, Cell 2023;186:1115
**Cure #4**
Dusseldorf
Jensen, Nat Med 2023;29:583
**Cure #5**
City of Hope
Dickter, NEJM 2024;390:669
**Cure #6** *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544
**Cure #7** *first Δ32 hetero donor
Berlin
Gaebler, Nature 2026;650:701
**Cure #8** *HIV rebound
Chicago
Rubinstein CROI 2025 #531
**Cure #9**
Oslo
Myhre Nat Micro 2026;11:1374



© 2026 Infectious Disease Board Review

## 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


## 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!



**rgulick@med.cornell.edu**





© 2026 Infectious Disease Board Review

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# ID Boards - Medical Content: 15% HIV

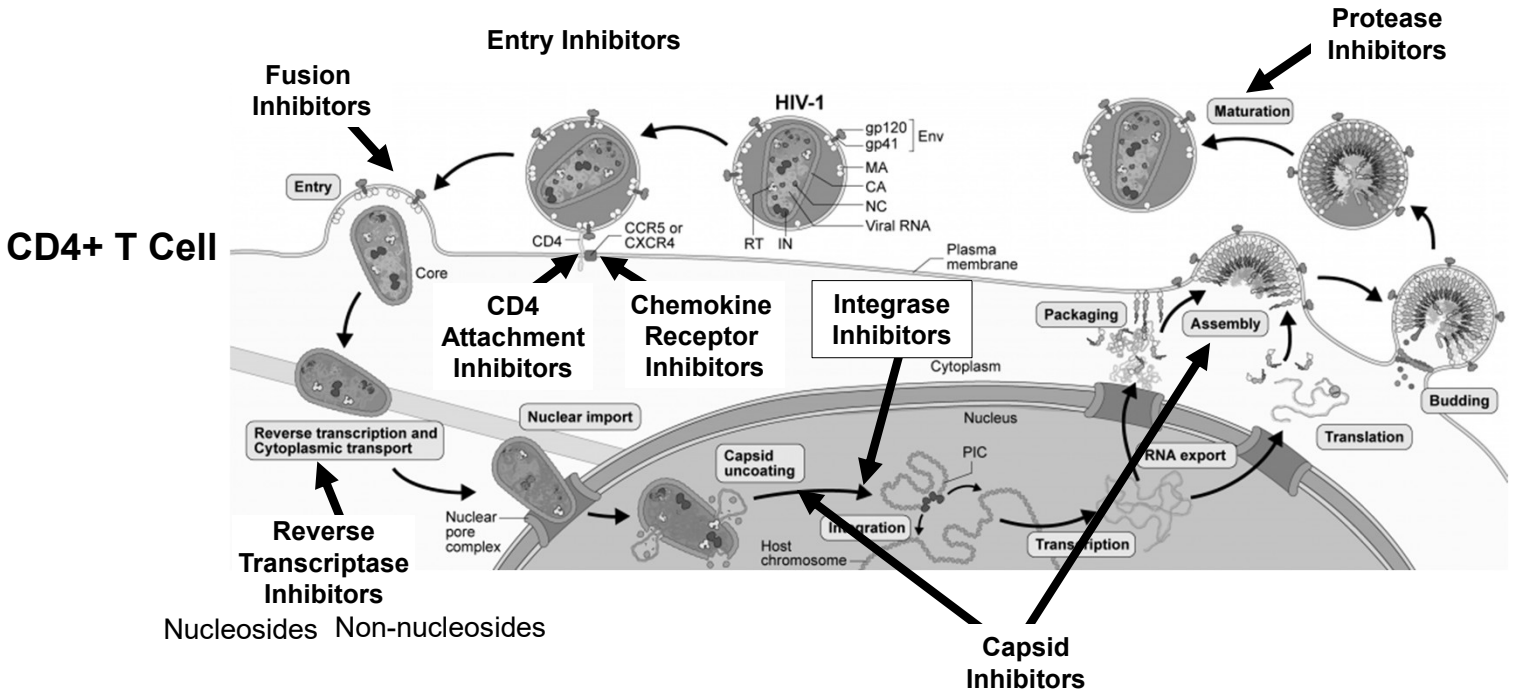
- Opportunistic Infections (5%)
  - Prevention
  - When to start ART with an OI
  - IRIS
  - Bacteria, Mycobacteria, Fungi, Parasites, Viruses
- Malignancies (<2%)
  - Kaposi sarcoma (KS)
  - Lymphoma
  - Cervical cancer
  - Anal cancer
- Other Complications of HIV (2%)
  - Heme, endocrine, GI, renal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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Life Cycle of HIV




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



© 2026 Infectious Disease Board Review

# Approved ART: 2026*

**Nucleoside/tide RTIs (NRTIs)**

- Zidovudine (ZDV, AZT)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Islatravir (ISL)
- 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, SQV, IDV, APV, FPV, + ENF (T-20) discontinued

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# 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; ↑CV/MI |
| **Zidovudine/ lamivudine** (ZDV/3TC) | No longer recommended | 1 tab bid | GI, anemia, lipoatrophy | Toxicity |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

# Choice of NNRTIs

| Drug | DHHS GL | Dose | Toxicities | Considerations |
|---|---|---|---|---|
| **Doravirine** (DOR) | Alternative | qd | ↓ CNS toxicity than EFV; ↓ lipids | TDF/FTC/DOR (1 pill, once-daily) |
| **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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

# 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

# Choice of Integrase Inhibitors

| Drug | DHHS GL | Dosing | Toxicities | Considerations |
|---|---|---|---|---|
| **Bictegravir** (BIC) | Recommended with TAF/FTC | 1 coform-ulated pill | Few, ↑creat, wt gain | TAF/FTC/BIC (1 pill, qd); ↑ barrier to resistance |
| **Dolutegravir** (DTG) | Recommended with (TAF or TDF)/(FTC or 3TC); alternative with ABC/3TC | 50 mg qd (bid with II resistance) | Few, ↑creat, CNS, wt gain | ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance |
| **Cabotegravir** (CAB) | Recommended for Δ with viro suppression | IM with IM RPV | Few | All injectable regimen |
| **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 |

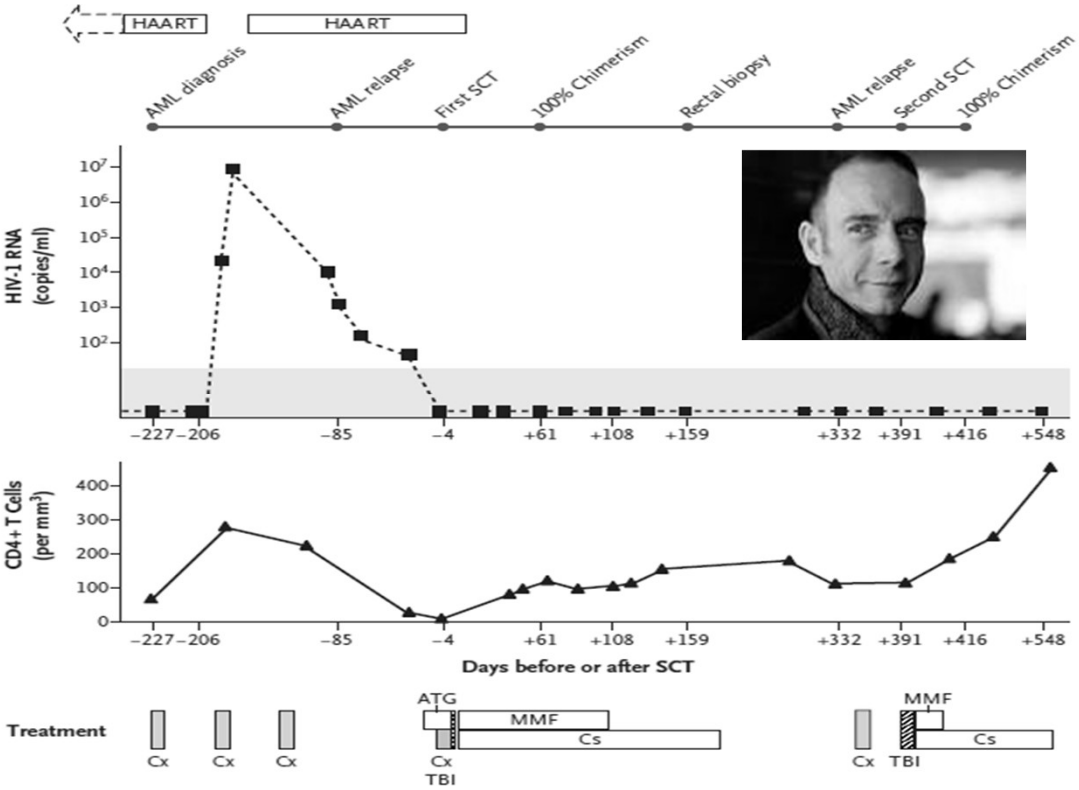
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Based on DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

# HIV Cure (N=1) 10+!




Hutter NEJM 2009;360:692

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**Cure #2** *first Latino
London
Gupta, Nature 2019;568:244
**Cure #3** *first woman
NYC
Hsu, Cell 2023;186:1115
**Cure #4**
Dusseldorf
Jensen, Nat Med 2023;29:583
**Cure #5**
City of Hope
Dickter, NEJM 2024;390:669
**Cure #6** *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544
**Cure #7** *first Δ32 hetero donor
Berlin
Gaebler, Nature 2026;650:701
**Cure #8** *HIV rebound
Chicago
Rubinstein CROI 2025 #531
**Cure #9**
Oslo
Myhre Nat Micro 2026;11:1374



© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**36**

# HIV Drug Resistance

**Michael Saag, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# HIV Drug Resistance

**Michael Saag, MD**
**University of Alabama at Birmingham**

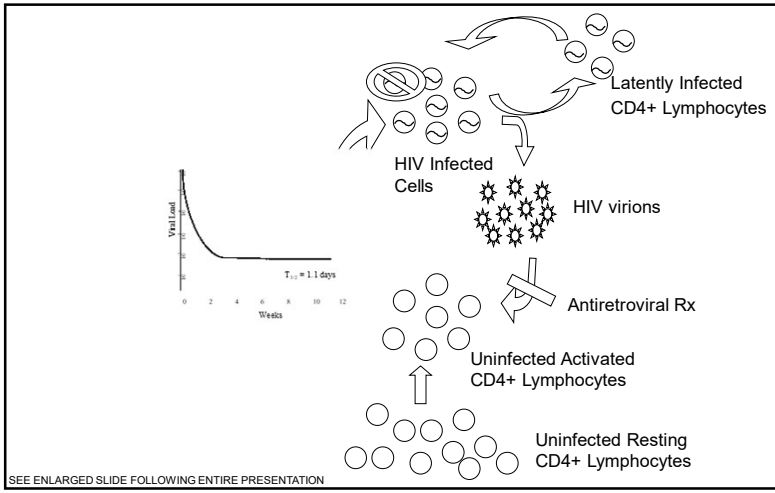
9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

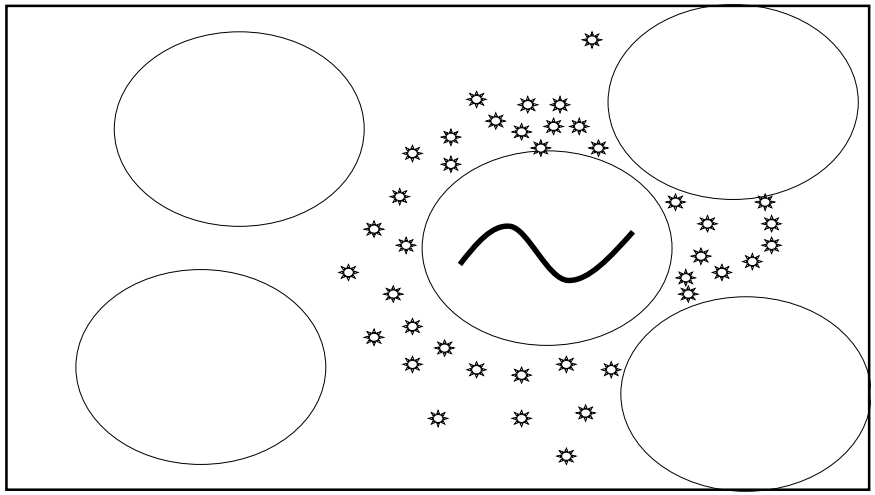
## How Does Resistance Happen?

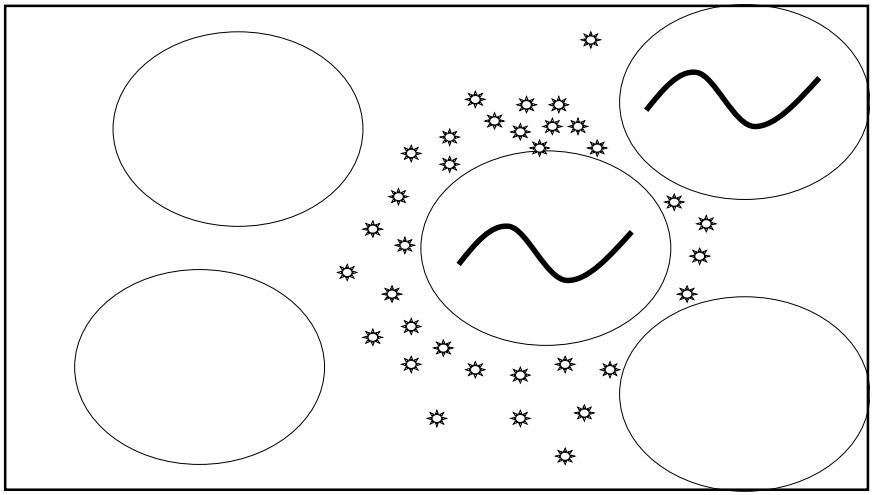


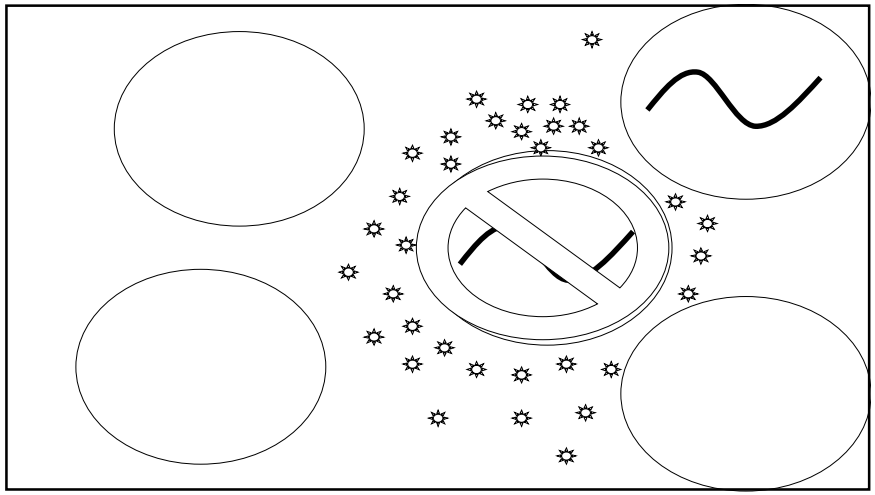

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

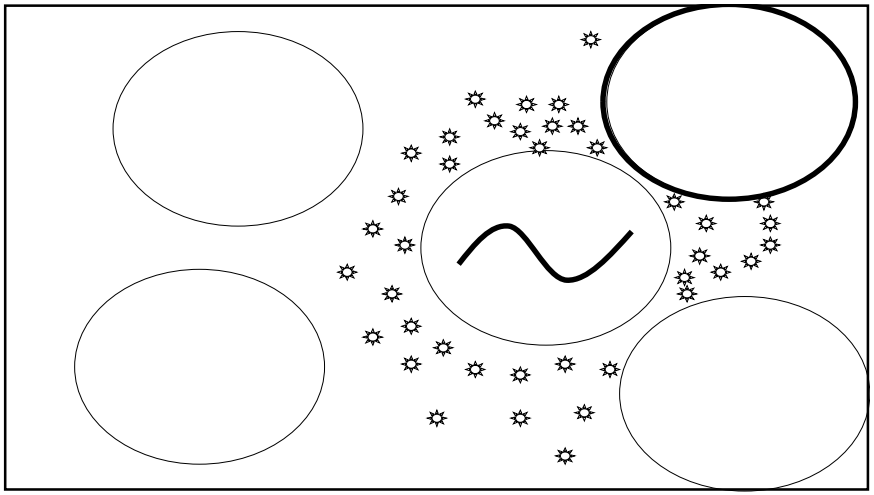


© 2026 Infectious Disease Board Review





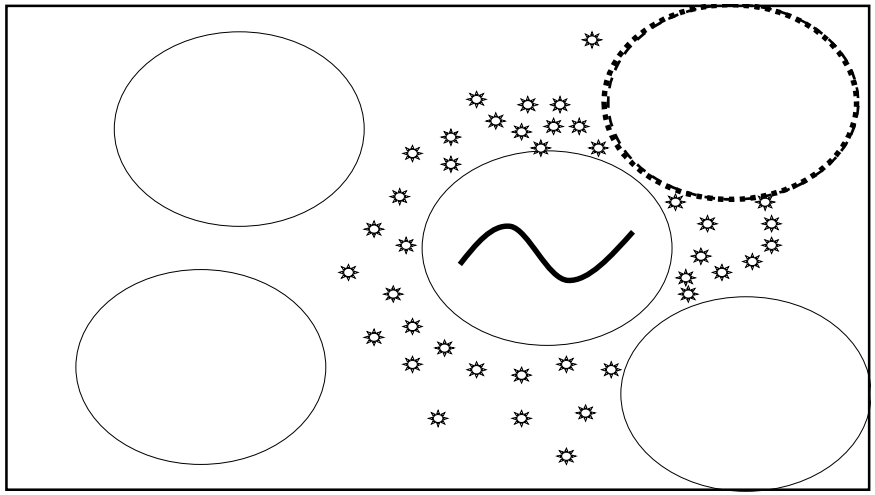


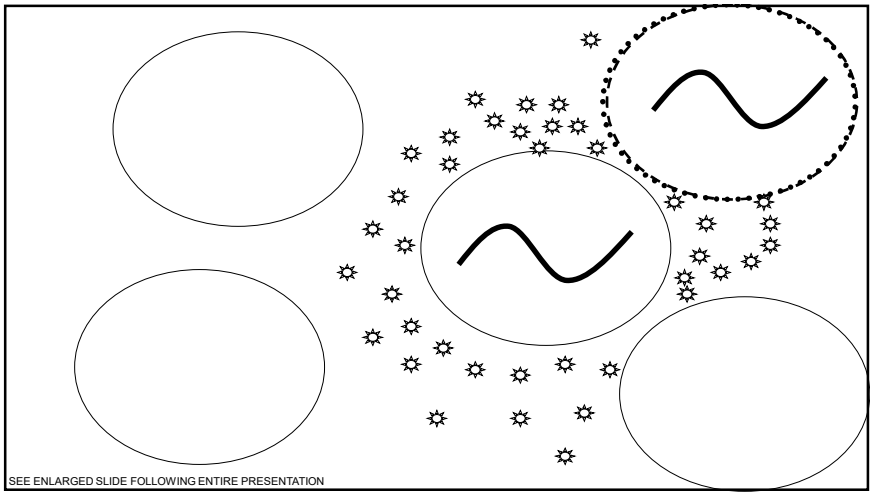


**36 HIV Drug Resistance**

*Speaker: Michael Saag, MD*

© 2026 Infectious Disease Board Review






## Resistance Testing

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

## Key Issues in HIV Resistance

**Easily Tested**
- Specific Mutations
- Cross – resistance
- Prevalence of resistance at baseline
- Role of archived DNA HIV virions

**Tough to Test**
- Definition of Phenotypes
- Complex resistance patterns
- Genetic Barrier
- Nuances of Resistance
- Relationship between Pk and Pd



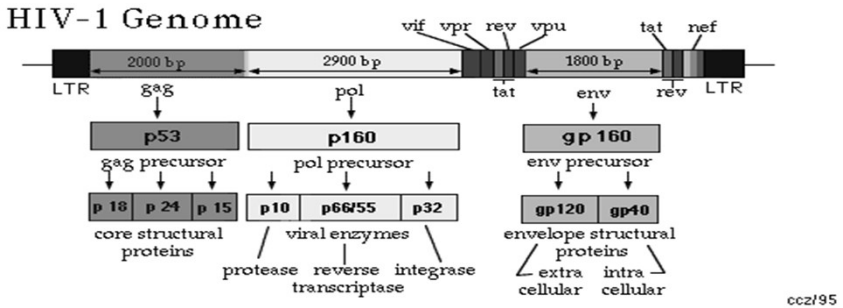
© 2026 Infectious Disease Board Review

## HIV Drug Resistance Testing

- HIV genotype as part of screening BEFORE ART is started
  AND
- Following failure of 1st or 2nd regimens
- 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 genotype result (more sensitive).

- NOTE WELL: Resistance mutations accrued from an earlier regimen MAY NOT be detected by tests obtained at the time of the current failing regimen

## HIV-1 Genome




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

↓

**M184V**

## Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

↓

**M184V**

**Wild-type amino acid (consensus)**

**Mutant amino acid**

**Table 1.** Amino acids and their abbreviations.

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

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

| Mutation | Selected By | Effects on Other NRTIs |
|---|---|---|
| **184V** | 3TC, FTC | - Loss of susceptibility to 3TC, FTC<br>- ↓ susceptibility to ABC, ddI (clinically insignificant)<br>- Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF |
| ~~TAMs~~ | AZT, d4T | - ↓ susceptibility to all NRTIs based on number of TAMs<br>- More resistance with 41/210/215 than 67/70/219 pathway |
| ~~151M, 69ins~~ | AZT/ddI, ddI/d4T | - Resistance to all NRTIs<br>- T69ins: TDF resistance |
| **K65R** | TDF, ABC, ddI | - Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC)<br>- ↑ susceptibility to AZT |
| ~~74V~~ | ABC, ddI | - ↓ susceptibility to ABC, ddI<br>- ↑ susceptibility to AZT, TDF |
| ~~44D, 118I~~ | AZT, d4T | -Increase NRTI resistance (with 41/210/215 pathway) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Question #1

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

## Question #1

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

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

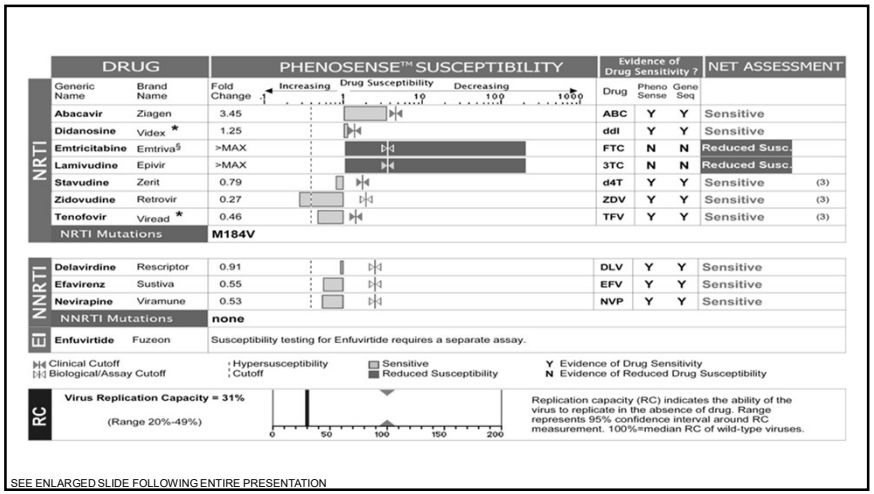
## Question #1

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

A. Efavirenz
B. Zidovudine
C. Tenofovir
D. Etravirine
**E. Emtricitabine***



© 2026 Infectious Disease Board Review



| DRUG | | PHENOSENSE™ SUSCEPTIBILITY | Evidence of Drug Sensitivity ? | | | NET ASSESSMENT | |
|---|---|---|---|---|---|---|---|
| Generic Name | Brand Name | Fold Change (Increasing Drug Susceptibility ← 1 10 100 1000 → Decreasing) | Drug | Pheno Sense | Gene Seq | | |
| NRTI | | | | | | | |
| Abacavir | Ziagen | 3.45 | ABC | Y | Y | Sensitive | |
| Didanosine | Videx * | 1.25 | ddI | Y | Y | Sensitive | |
| Emtricitabine | Emtriva§ | >MAX | FTC | N | N | Reduced Susc. | |
| Lamivudine | Epivir | >MAX | 3TC | N | N | Reduced Susc. | |
| Stavudine | Zerit | 0.79 | d4T | Y | Y | Sensitive | (3) |
| Zidovudine | Retrovir | 0.27 | ZDV | Y | Y | Sensitive | (3) |
| Tenofovir | Viread * | 0.46 | TFV | Y | Y | Sensitive | (3) |
| NRTI Mutations | | M184V | | | | | |
| NNRTI | | | | | | | |
| Delavirdine | Rescriptor | 0.91 | DLV | Y | Y | Sensitive | |
| Efavirenz | Sustiva | 0.55 | EFV | Y | Y | Sensitive | |
| Nevirapine | Viramune | 0.53 | NVP | Y | Y | Sensitive | |
| NNRTI Mutations | | none | | | | | |
| EI | | | | | | | |
| Enfuvirtide | Fuzeon | Susceptibility testing for Enfuvirtide requires a separate assay. | | | | | |

Clinical Cutoff / Biological/Assay Cutoff — Hypersusceptibility Cutoff — Sensitive / Reduced Susceptibility — Y Evidence of Drug Sensitivity / N Evidence of Reduced Drug Susceptibility

RC: Virus Replication Capacity = 31% (Range 20%-49%) (0 50 100 150 200)

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%=median RC of wild-type viruses.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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

## Question #2

**The genotype shows an a K65R mutation. Which RTI drugs would you include?**

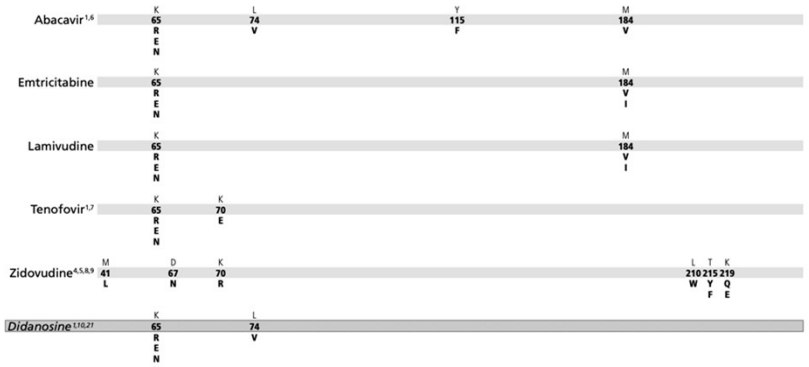
A. ZDV
B. TDF
C. ddI
D. ABC
E. Islatravir

## Question #2

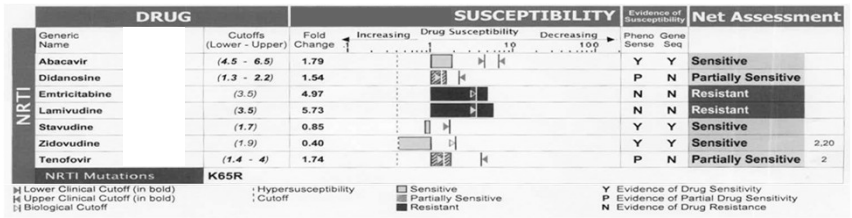
**The genotype shows an a K65R mutation. Which RTI drugs would you include?**

A. ZDV
B. TDF
C. ddI
D. ABC
**E. Islatravir***


© 2026 Infectious Disease Board Review




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

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

## Question #3

- 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


© 2026 Infectious Disease Board Review

## Question #3

**Which of the following mutations indicate high level resistance to elvitegravir?**

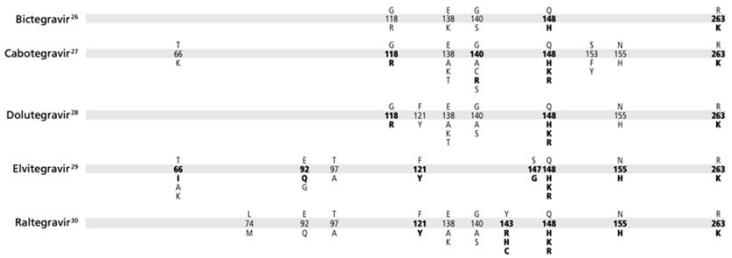
A. Q148R
B. L68I
C. L68V
D. K67N
E. K65R

## Question #3

**Which of the following mutations indicate high level resistance to elvitegravir?**

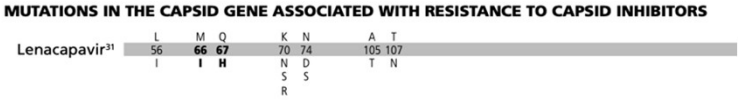
**A. Q148R***
B. L68I
C. L68V
D. K67N
E. K65R

## InSTI Resistance Mutations




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Lenacapavir Resistance Mutations




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## 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 Positive
- HIV RNA 766 c/ml

## Question #4

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

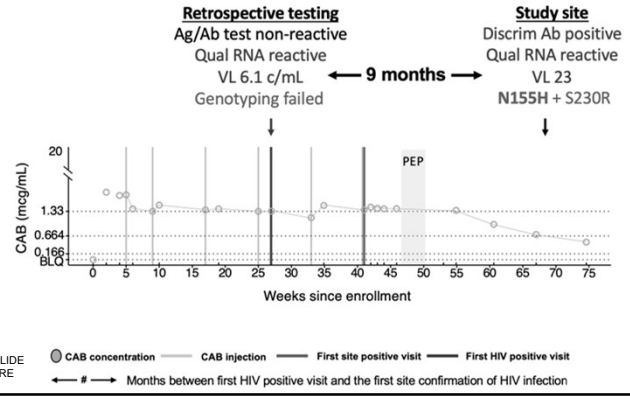
A. S147G
B. N155H
C. Y143R
D. E92Q
E. K65R

## 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

## Case Study: Confirmation of Infection

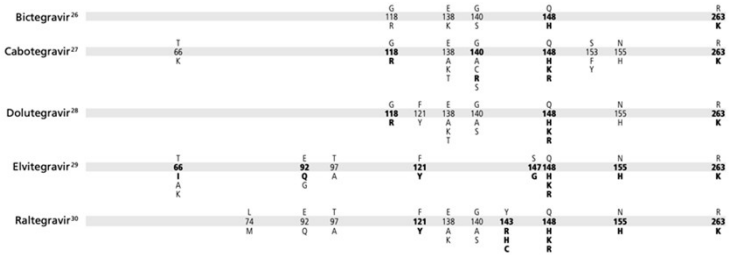



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## InSTI Resistance Mutations




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Question #5

- 34-year-old woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD 482 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

## Question #5

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

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

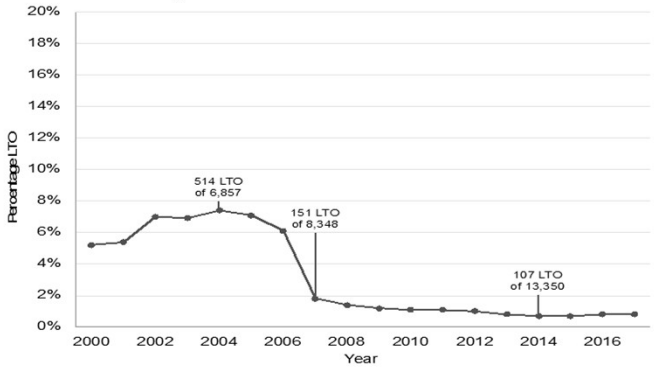
## Question #5

**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%


© 2026 Infectious Disease Board Review

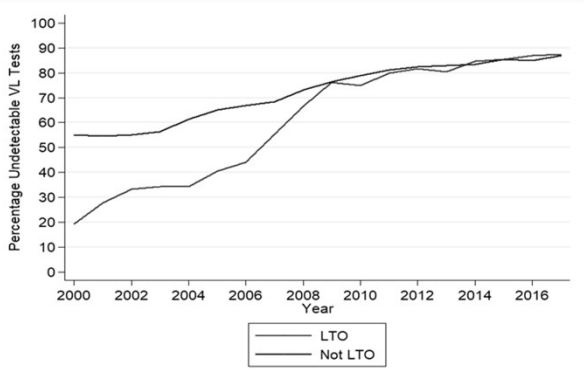
## Prevalence of Patients with Limited Treatment Options




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Crane et al, IAS 2019

## Virologic Success in Those with or without LTO




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Crane et al, IAS 2019

## Common Mutations To Memorize

| | |
|---|---|
| • M184V/I | 3TC and FTC |
| • M41L, D67N, K70R,L210W, T215Y, K219Q<br>4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides | "TAMS" |
| • K65R | Islatravir, Tenofovir |
| | |
| • K103N | EFV (and NVP) |
| | |
| • Y181C | NVP and other NNRTI |
| • E138K, K101E | RPV and other NNRTI |
| | |
| • I50L | ATV |
| | |
| • N155H, Q148H/R/K | RAL and EVG |
| • Y143C | RAL |
| • R263K | DTG |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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



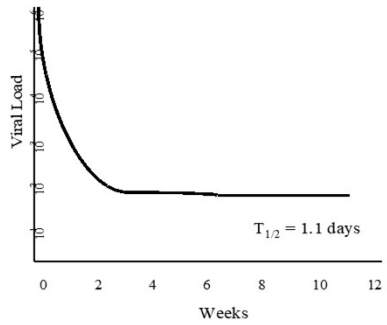


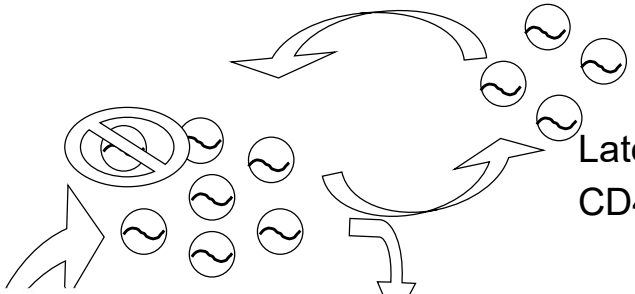
© 2026 Infectious Disease Board Review

**msaag@uabmc.edu**



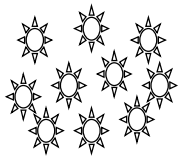
© 2026 Infectious Disease Board Review



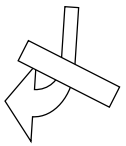



Latently Infected
CD4+ Lymphocytes

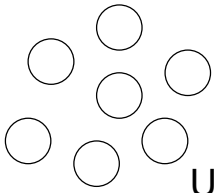
HIV Infected
Cells



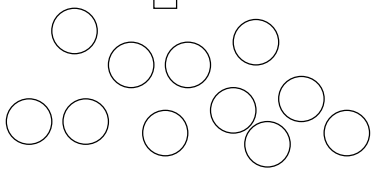
HIV virions



Antiretroviral Rx



Uninfected Activated
CD4+ Lymphocytes



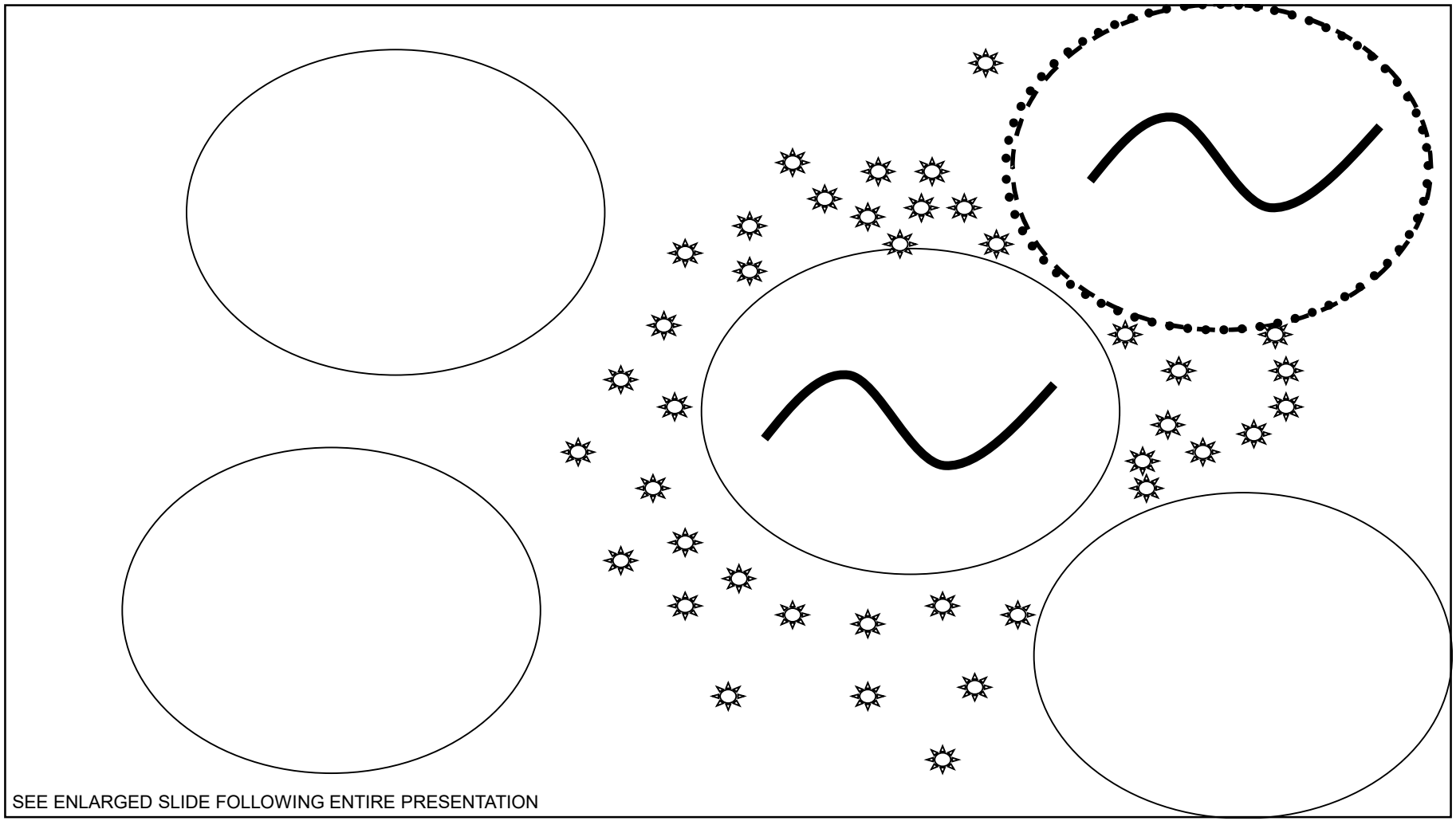
Uninfected Resting
CD4+ Lymphocytes

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**36 HIV Drug Resistance**

*Speaker: Michael Saag, MD*

© 2026 Infectious Disease Board Review

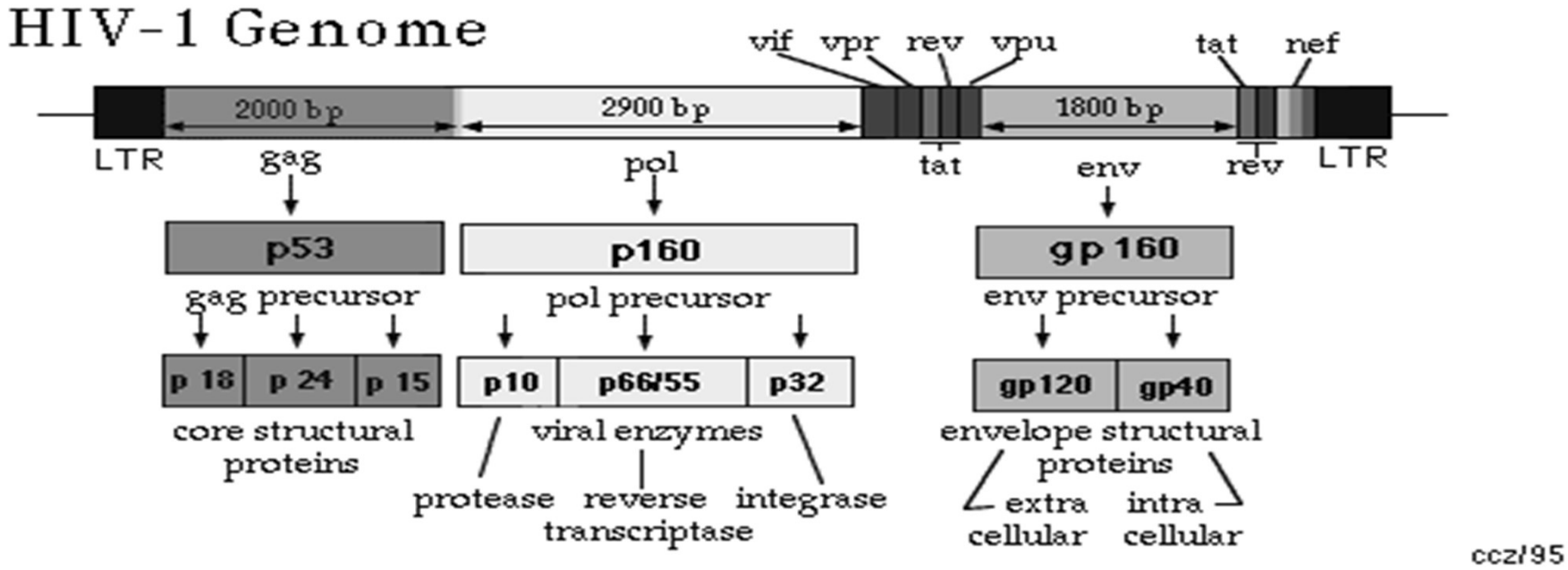



**36 HIV Drug Resistance**

*Speaker: Michael Saag, MD*

© 2026 Infectious Disease Board Review

# HIV-1 Genome



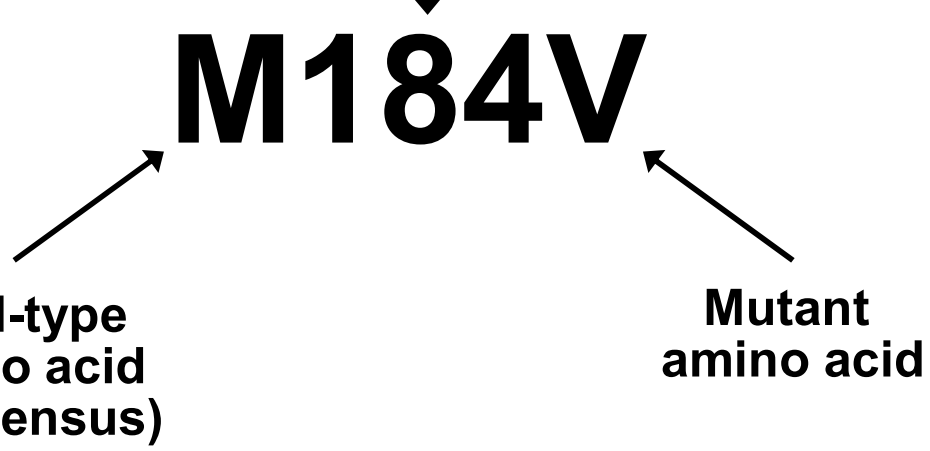

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**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 |


© 2026 Infectious Disease Board Review

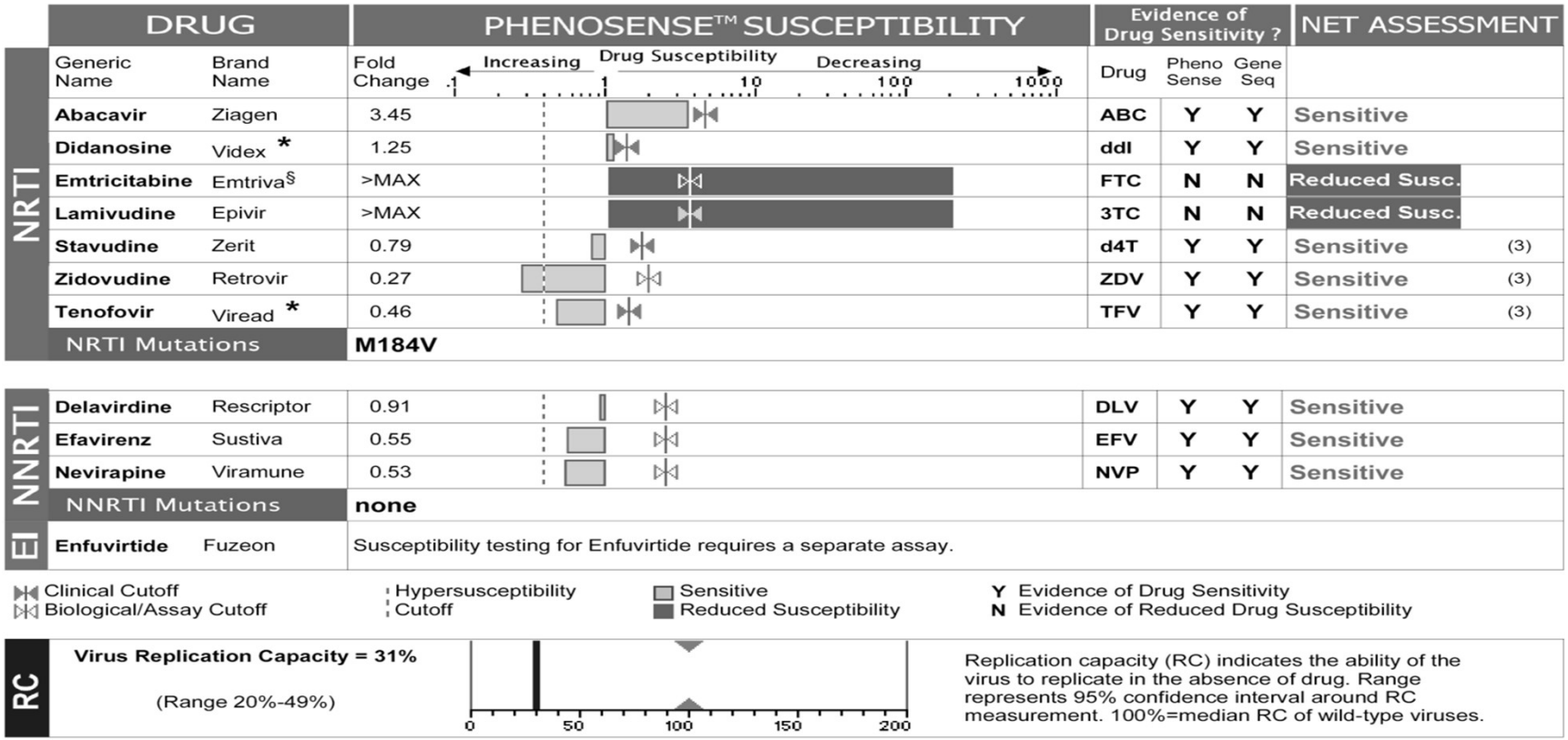
# Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

| Mutation | Selected By | Effects on Other NRTIs |
|---|---|---|
| **184V** | 3TC, FTC | - Loss of susceptibility to 3TC, FTC<br>- ↓ susceptibility to ABC, ddI (clinically insignificant)<br>- Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF |
| ~~TAMs~~ | AZT, d4T | - ↓ susceptibility to all NRTIs based on number of TAMs<br>- More resistance with 41/210/215 than 67/70/219 pathway |
| ~~151M, 69ins~~ | AZT/ddI, ddI/d4T | - Resistance to all NRTIs<br>- T69ins: TDF resistance |
| **K65R** | TDF, ABC, ddI | - Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC)<br>- ↑ susceptibility to AZT |
| ~~74V~~ | ABC, ddI | - ↓ susceptibility to ABC, ddI<br>- ↑ susceptibility to AZT, TDF |
| ~~44D, 118I~~ | AZT, d4T | -Increase NRTI resistance (with 41/210/215 pathway) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

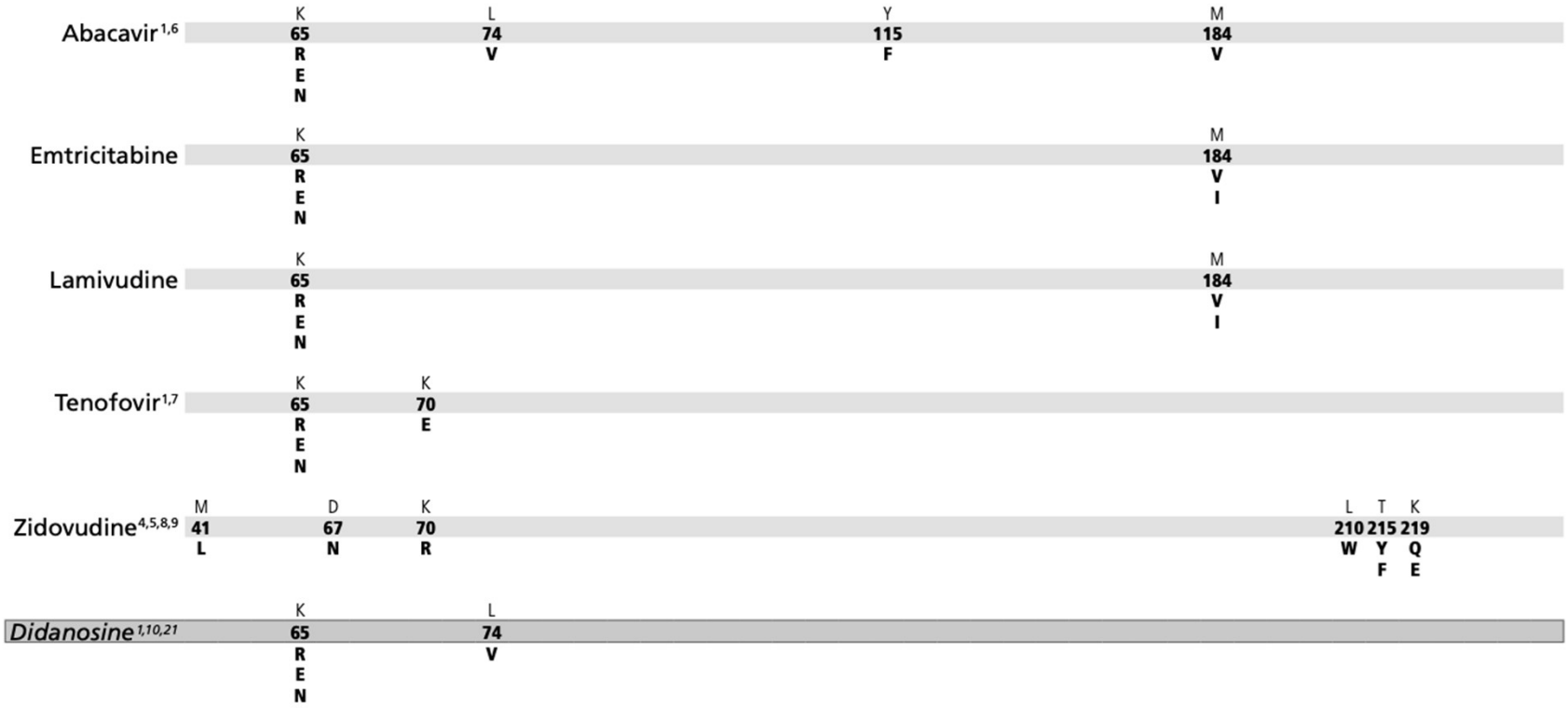



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**36 HIV Drug Resistance**

*Speaker: Michael Saag, MD*

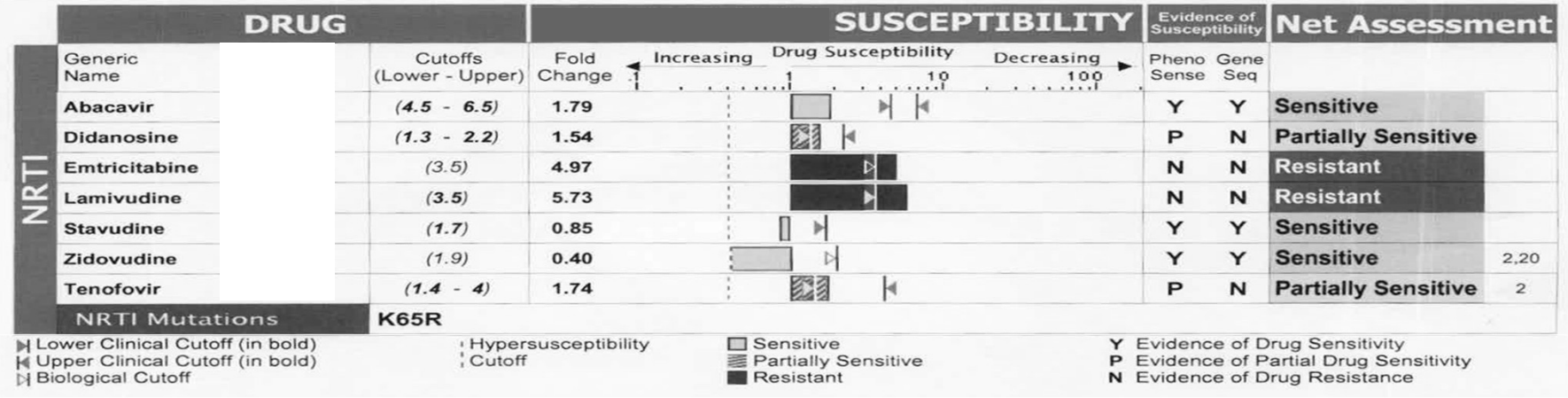
© 2026 Infectious Disease Board Review




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review



| | DRUG | | SUSCEPTIBILITY | | Evidence of Susceptibility | | Net Assessment | |
|---|---|---|---|---|---|---|---|---|
| | Generic Name | Cutoffs (Lower - Upper) | Fold Change | Increasing ← Drug Susceptibility → Decreasing (.1 / 1 / 10 / 100) | Pheno Sense | Gene Seq | | |
| NRTI | **Abacavir** | ***(4.5 - 6.5)*** | **1.79** | | **Y** | **Y** | **Sensitive** | |
| | **Didanosine** | ***(1.3 - 2.2)*** | **1.54** | | **P** | **N** | **Partially Sensitive** | |
| | **Emtricitabine** | *(3.5)* | **4.97** | | **N** | **N** | **Resistant** | |
| | **Lamivudine** | ***(3.5)*** | **5.73** | | **N** | **N** | **Resistant** | |
| | **Stavudine** | ***(1.7)*** | **0.85** | | **Y** | **Y** | **Sensitive** | |
| | **Zidovudine** | *(1.9)* | **0.40** | | **Y** | **Y** | **Sensitive** | 2,20 |
| | **Tenofovir** | ***(1.4 - 4)*** | **1.74** | | **P** | **N** | **Partially Sensitive** | 2 |
| | **NRTI Mutations** | **K65R** | | | | | | |

Lower Clinical Cutoff (in bold)
Upper Clinical Cutoff (in bold)
Biological Cutoff

Hypersusceptibility Cutoff

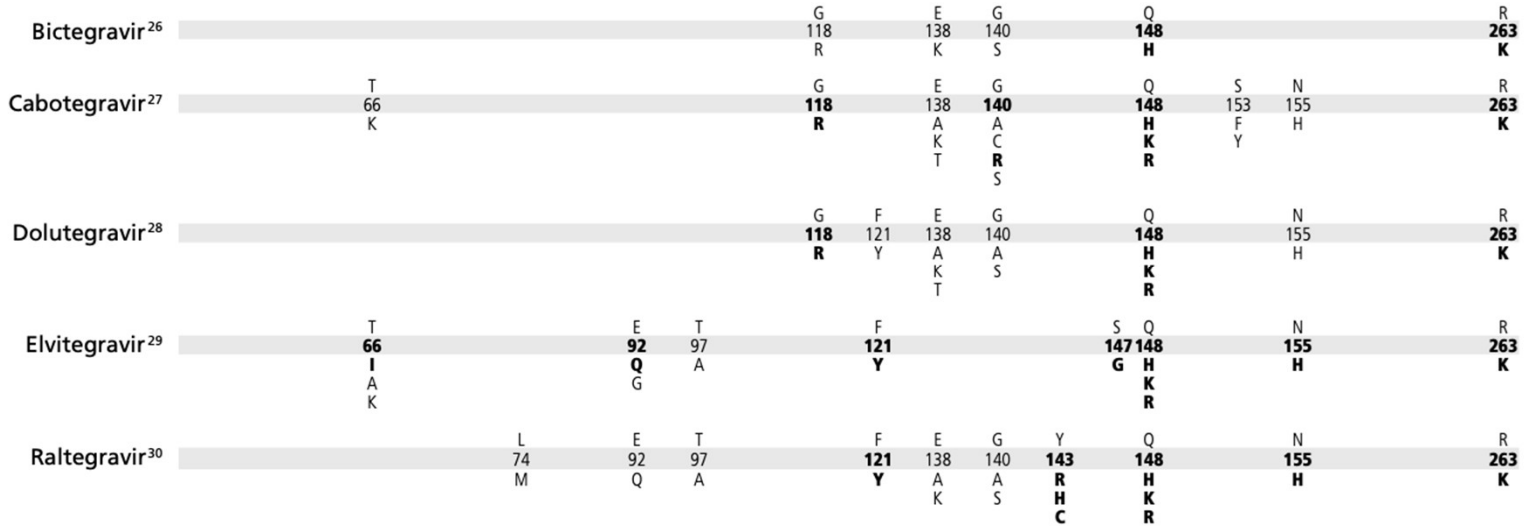
Sensitive
Partially Sensitive
Resistant

Y Evidence of Drug Sensitivity
P Evidence of Partial Drug Sensitivity
N Evidence of Drug Resistance

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# InSTI Resistance Mutations




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# 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 | | | |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



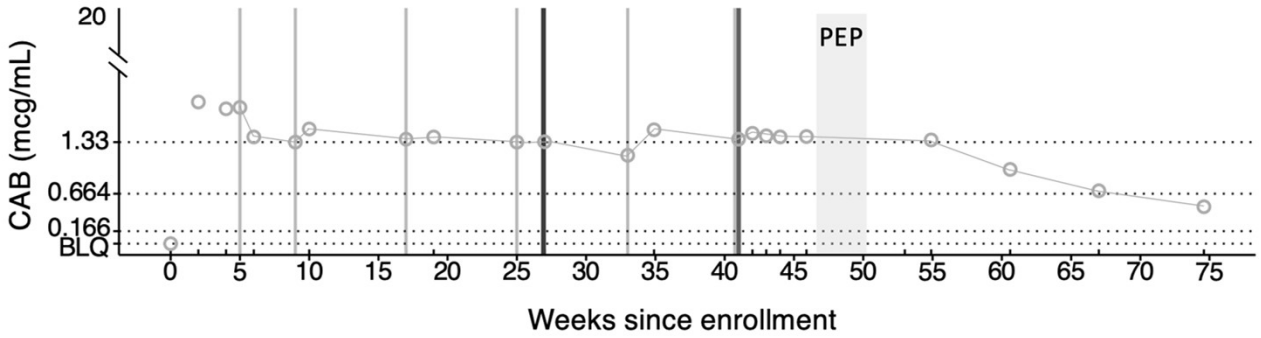
© 2026 Infectious Disease Board Review

# Case Study: Confirmation of Infection

**Retrospective testing**
Ag/Ab test non-reactive
Qual RNA reactive
VL 6.1 c/mL
Genotyping failed

← 9 months →

**Study site**
Discrim Ab positive
Qual RNA reactive
VL 23
**N155H** + S230R




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

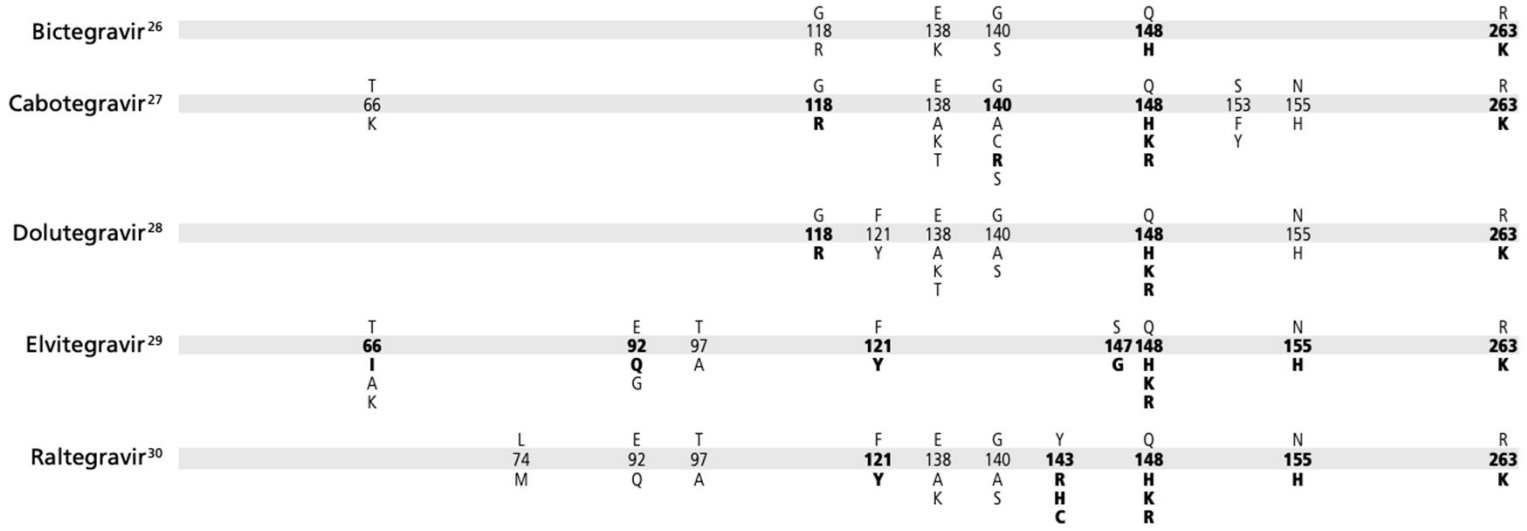
CAB concentration — CAB injection — First site positive visit — First HIV positive visit

← # → Months between first HIV positive visit and the first site confirmation of HIV infection



© 2026 Infectious Disease Board Review

# InSTI Resistance Mutations

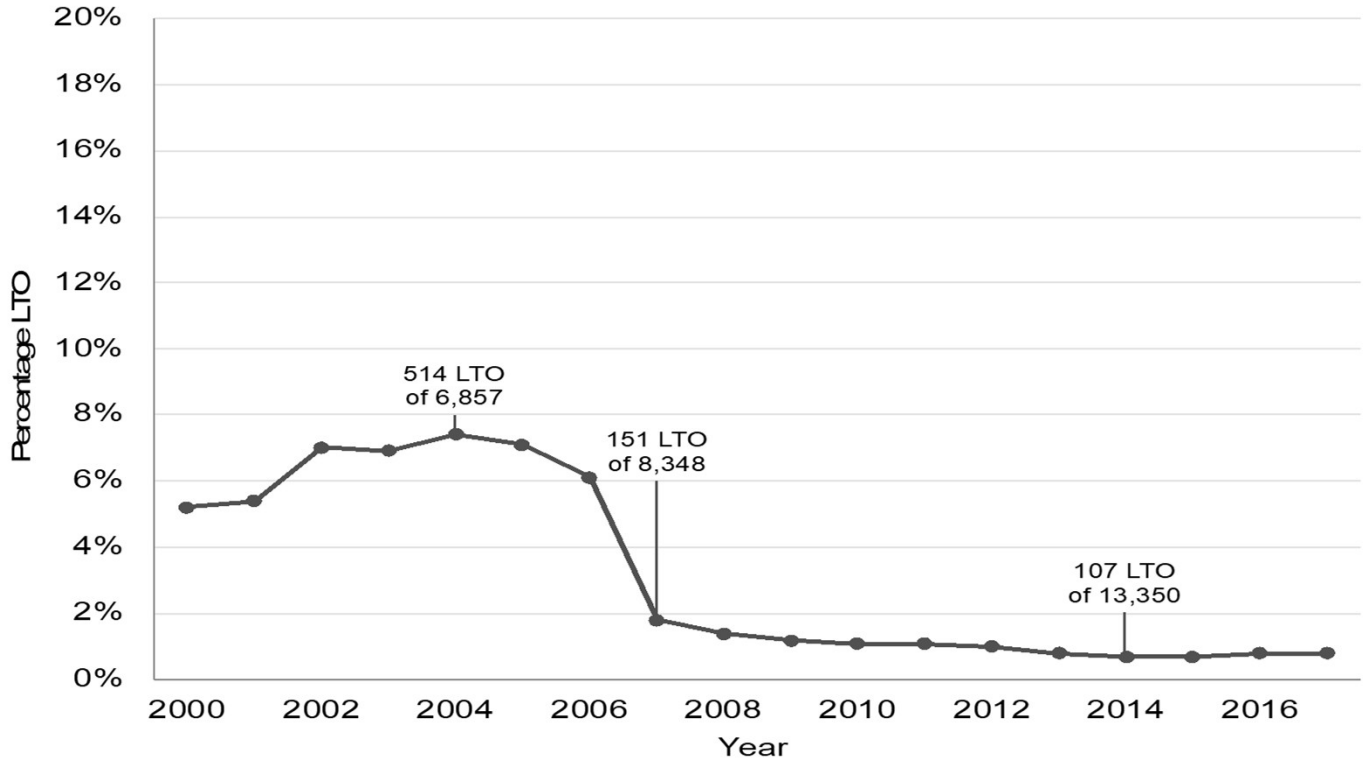



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Prevalence of Patients with Limited Treatment Options



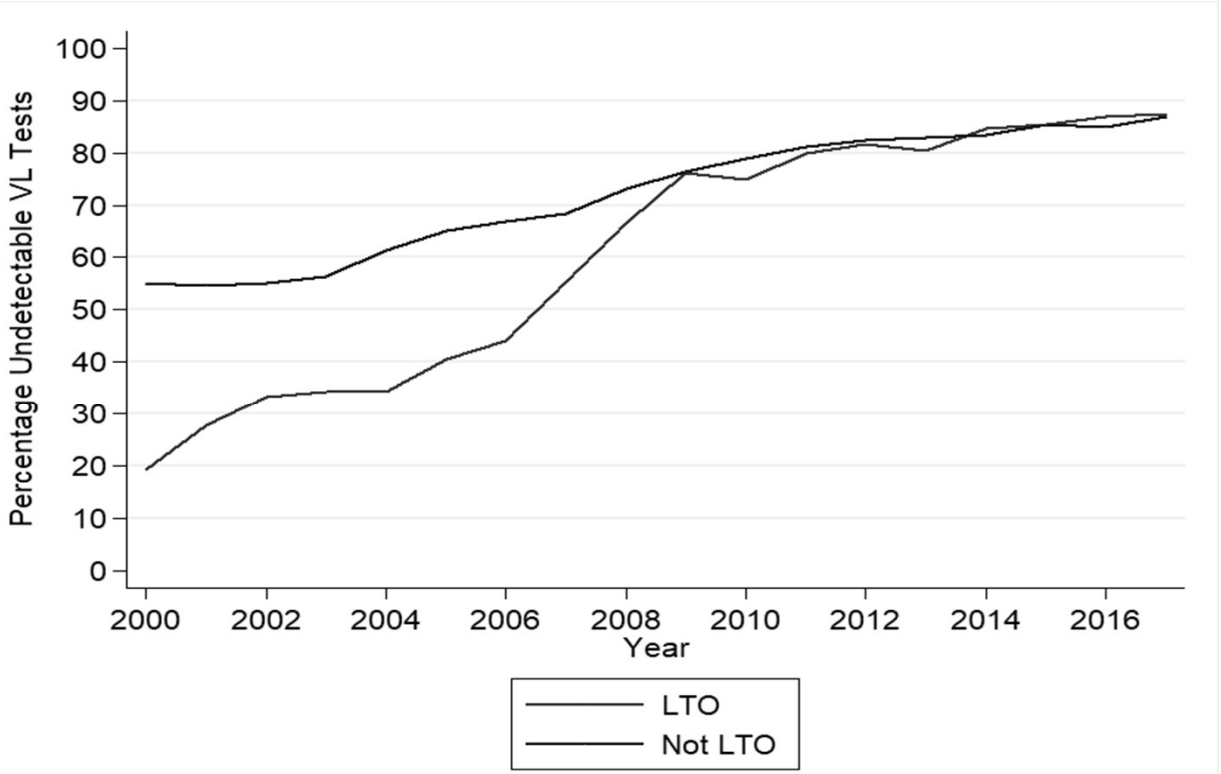

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Crane et al, IAS 2019



© 2026 Infectious Disease Board Review

# Virologic Success in Those with or without LTO




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Crane et al, IAS 2019



© 2026 Infectious Disease Board Review

# Common Mutations To Memorize

| | |
|---|---|
| • M184V/I | 3TC and FTC |
| • M41L, D67N, K70R,L210W, T215Y, K219Q<br>4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides | ”TAMS” |
| • K65R | Islatravir, Tenofovir |
| | |
| • K103N | EFV (and NVP) |
| | |
| • Y181C | NVP and other NNRTI |
| • E138K, K101E | RPV and other NNRTI |
| | |
| • I50L | ATV |
| | |
| • N155H, Q148H/R/K | RAL and EVG |
| • Y143C | RAL |
| • R263K | DTG |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**37**

# Antiretroviral Therapy for Special Populations

**Roy Gulick, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Antiretroviral Therapy (ART) for Special Populations

**Roy M. Gulick, MD, MPH**
**Weill Cornell Medicine**

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Special Populations

- Acute/recent HIV infection
- Acute opportunistic infection
- Tuberculosis
- HIV-HBV co-infection
- HIV-HCV co-infection
- Pregnancy
- Post-HIV exposure (PEP)
  - Occupational (oPEP)
  - Non-occupational (nPEP)
- Pre-HIV exposure (PrEP)

## Question #1

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



© 2026 Infectious Disease Board Review

## Question #1

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

## Acute or Recent HIV

- ART is RECOMMENDED.
- ART reduces symptoms and signs and reduces transmission.
- Long-term virologic, immunologic, and clinical data sparse.
- 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 9/25/25

## 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

## 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.

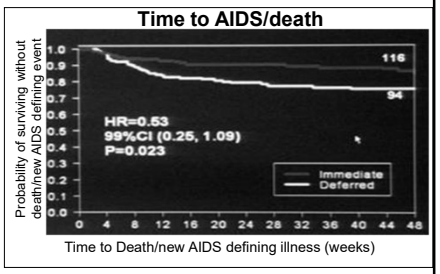
### When should she start ART?

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


© 2026 Infectious Disease Board Review

## 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)




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Zolopa PLoS One 2009;4:e5575

## HIV-TB Co-infection

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

DHHS Guidelines 9/25/25

## 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

## 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



© 2026 Infectious Disease Board Review

## 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 twice daily)
    - 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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

DHHS Guidelines 9/25/25

## 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)

## 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)***

## HIV-HBV Co-infection

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

DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

## 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 9/25/25

## Question #5

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

## Question #5

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***

## Antiretrovirals in Pregnancy

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

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>


© 2026 Infectious Disease Board Review

## ART in Pregnancy: NRTI

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

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>

## ART in Pregnancy: NNRTI

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

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>

## 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)

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>

## ART in Pregnancy: INSTI

- Preferred (with TAF or TDF / 3TC or FTC):
  - Bictegravir
  - Dolutegravir (neural tube defects NOT significantly ↑ vs. other ART)
- Alternative:
  - Dolutegravir/lamivudine (2-drug regimen)
  - Raltegravir (need to use bid)
- Not recommended:
  - Elvitegravir/cobicistat (↓ drug concentrations)
  - IM cabotegravir + rilpivirine (could continue if already taking)

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>


© 2026 Infectious Disease Board Review

## ART in Pregnancy: Other

- Not recommended:
  - Cobicistat as a booster (for EVG or PIs)
- Only recommended for treatment-experienced:
  - Etravirine, fostemsavir, ibalizumab, lenacapavir, maraviroc

DHHS Perinatal Guidelines 3/31/26 <www.clinicalinfo.hiv.gov>

## Question #6

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

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

A. Tenofovir (TDF 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 TAF)/emtricitabine + protease inhibitor

## 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 TAF)/emtricitabine + protease inhibitor

## Antiretrovirals for PEP (Post-Exposure Prophylaxis)

- Assess exposure: source fluid, volume of fluid, type of exposure, timing
- Assess exposure source: HIV and hepatitis testing
- Testing
  - Baseline: HIV Ag/Ab test, HBV, pregnancy, + creatinine and AST/ALT (f/up only for abnormal results or clinical indications)
  - Follow-up (4-6 weeks; only if PEP started >24 hours after exposure or missed PEP doses): HIV Ag/Ab and HIV RNA
  - Follow-up (12 weeks): HIV Ag/Ab and HIV RNA
- Offer 4 weeks of PEP for recognized transmission risk
  - Start ASAP (within 72 hours; adjust regimen for possibility of drug resistance)
    - **Preferred: BIC**/TAF/FTC or **DTG** + (TAF or TDF)/(FTC or 3TC)
    - **Alternative: DRV/r or /c** + (TAF or TDF)/(FTC or 3TC)
  - F/u within 72 hours

CDC Kofman ICHE 2025:1-11 (occupational); CDC Tanner MMWR 2025;74:1-56 (non-occupational)


© 2026 Infectious Disease Board Review

## 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

## 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

## 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)
  - SC lenacapavir every 6 months for ♂ and ♀
  - Provide risk reduction, adherence counseling, condoms
- On PrEP:
  - HIV testing every 3-4 months, monitor CrCl every 6 (age >50 or CrCl <90) or 12 months
  - Risk reduction, condoms, STI assessments/treatment + evaluate need to continue PrEP

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

## Conclusions

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



© 2026 Infectious Disease Board Review

## Acknowledgments


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

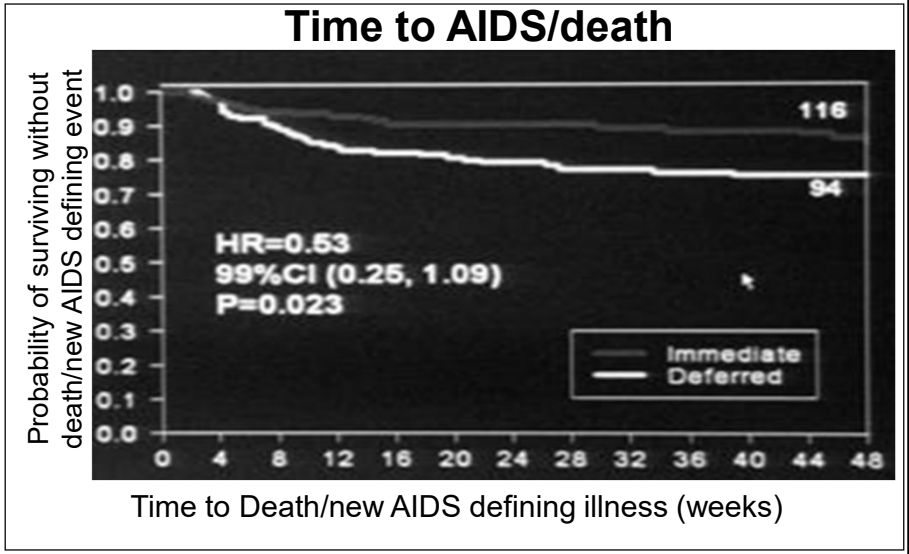

rgulick@med.cornell.edu



© 2026 Infectious Disease Board Review

# 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)




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Zolopa PLoS One 2009;4:e5575



© 2026 Infectious Disease Board Review

# 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 twice daily)
    - 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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

DHHS Guidelines 9/25/25



© 2026 Infectious Disease Board Review

# 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)
  - SC lenacapavir every 6 months for ♂ and ♀
  - Provide risk reduction, adherence counseling, condoms
- On PrEP:
  - HIV testing every 3-4 months, monitor CrCl every 6 (age >50 or CrCl <90) or 12 months
  - Risk reduction, condoms, STI assessments/treatment + evaluate need to continue PrEP

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

**BR4**

# Board Review Day 4

**Drs. Gulick (Moderator),
Bloch, Gandhi, Kotton, Maldarelli,
Masur, Saag, and Whitley**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Board Review: Day 4

**Moderator: Roy M. Gulick, MD**

**Faculty: Drs. Bloch, Gandhi, Kotton, Maldarelli, Saag, and Whitley**

7/28/2026



**#46** **An 86-year-old female is admitted with right wrist pain and fever.**

**She was hospitalized the preceding week for pyelonephritis with urine cultures growing *Escherichia coli*, with negative blood cultures. She was discharged on a 7-day course of ciprofloxacin.**

**She lives with her granddaughter and 2 cats.**

**The wrist was aspirated with 23,000 WBC/mm$^3$ (94% neutrophiles) but negative Gram stain and crystal exam.**





**#46** **Empiric vancomycin and ceftriaxone were started, and she was taken to the operating room for right wrist arthrotomy with finding of purulent fluid in the midcarpal and radiocarpal joints.**

**On hospital day 2 she continued to be febrile with ongoing right wrist pain. On hospital day 3, she noted new onset of left wrist pain. Imaging shows chondrocalcinosis of the wrist.**

**Cultures from the arthrocentesis, operative cultures, and blood cultures are all no growth at 72 hours.**





**#46** **What is the most likely cause of her polyarticular arthritis?**

A. ***E. coli*** **bacteremia with secondary septic arthritis**
B. ***Borrelia burgdorferi*** **infection**
C. ***Bartonella henselae*** **infection**
D. **Parvovirus B19 infection**
E. **Calcium pyrophosphate deposition disease**



**BR4 Board Review Questions - Day 4**

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#46** **What is the most likely cause of her polyarticular arthritis?**

A. *E. coli* bacteremia with secondary septic arthritis
B. *Borrelia burgdorferi* infection
C. *Bartonella henselae* infection
D. Parvovirus B19 infection
E. Calcium pyrophosphate deposition disease**

4 of 4

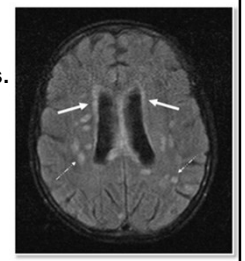
BOARD REVIEW DAY 4

**#47** **A 32-year-old female with HIV infection (viral load 100,000/ml, and a CD4 count below 10 cells/mm$^3$) has failed all available ART regimens.**

**Her mother brings her to the clinic because of confusion for 1-2 weeks. She is afebrile, oriented x 1, and slow to respond.**

**She has nystagmus and cranial nerve VI palsy on the right.**

**The contrast enhanced MRI image (shown below) is read as showing ventriculitis (i.e., inflammation of the ependymal lining of the lateral cerebral ventricles).**



1 of 3

BOARD REVIEW DAY 4

**#47** **Which PCR of CSF would most likely provide the most likely diagnosis?**

A. JC virus
B. Epstein-Barr virus
C. Cytomegalovirus
D. Human herpesvirus 6
E. Human herpesvirus 8

2 of 3

BOARD REVIEW DAY 4

**#47** **Which PCR of CSF would most likely provide the most likely diagnosis?**

A. JC virus
B. Epstein-Barr virus
C. Cytomegalovirus**
D. Human herpesvirus 6
E. Human herpesvirus 8

3 of 3

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#48** A 43-year-old man with HIV on a dolutegravir-based regimen with excellent virologic response (CD4 720 cells/µL, HIV RNA <20 copies/mL repeatedly for years) presents for routine follow-up and is found to have a CD4 count of 456 cells/µL and viral load 10,000 copies/ml.

He states he has not missed a single dose of his antiretrovirals and did not start any new medications.

One month ago, he started a nutritional supplement from a health food store called "Vitamin-Mineral Boost" that he started before he goes to bed, the same time as he takes his antiretrovirals.

1 of 3

BOARD REVIEW DAY 4

**#48** What is the most likely cause of his elevated viral load level?

A. Poor adherence
B. Taking the antiretrovirals with food
C. Calcium/magnesium in the nutritional supplement
D. Vitamin B6 in the nutritional supplement

2 of 3

BOARD REVIEW DAY 4

**#48** What is the most likely cause of his elevated viral load level?

A. Poor adherence
B. Taking the antiretrovirals with food
C. Calcium/magnesium in the nutritional supplement**
D. Vitamin B6 in the nutritional supplement

3 of 3

BOARD REVIEW DAY 4

**#49** A 53-year-old man has received CAR CD19 T cell therapy with axicabtagene ciloleucel (Yescarta - a CD19-directed genetically modified autologous T cell immunotherapy) for refractory diffuse large B cell lymphoma (DLBCL). He had failed prior regimens of standard chemotherapy.

Seven days after infusion of the axicabtagene ciloleucel (Yescarta), he developed fever to 38.3°C, hypotension, hypoxemia, pulmonary infiltrates, and oliguria.

On physical examination, other than his vital signs there are no new findings other than diffuse crackles. He has a port in place that looks unremarkable.

His absolute neutrophil count in 50 cells/µl.

1 of 3

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#49** **Which of the following would most accurately describe how to distinguish septic shock from a CAR-T cell cytokine release syndrome in this patient?**

A. IL-1 level
B. IL-6 level
C. CH50
D. C reactive protein
E. There is currently no clinical or laboratory test that will distinguish sepsis from CAR-T cytokine release syndrome

2 of 3

BOARD REVIEW DAY 4

**#49** **Which of the following would most accurately describe how to distinguish septic shock from a CAR-T cell cytokine release syndrome in this patient?**

A. IL-1 level
B. IL-6 level
C. CH50
D. C reactive protein
E. There is currently no clinical or laboratory test that will distinguish sepsis from CAR-T cytokine release syndrome**

3 of 3

BOARD REVIEW DAY 4

**#50** **A 62-year-old man with newly diagnosed HIV infection (HIV RNA 326,000 copies/ml, CD4 205 cells/μL) starts antiretroviral therapy with tenofovir alafenamide (TAF)/emtricitabine/bictegravir. At 3 months, he had an HIV RNA is <20 copies/ml and CD4 211 cells/μL.**

**At 6 months, HIV RNA <20 copies/ml and CD4 203 cells/μL.**

**He's concerned about his CD4 cell count.**

1 of 3

BOARD REVIEW DAY 4

**#50** **What do you recommend?**

A. Continue present ART regimen
B. Change TAF/emtricitabine to ABC/lamivudine
C. Change bictegravir to darunavir/ritonavir
D. Add darunavir/ritonavir
E. Start filgrastim (G-CSF)

2 of 3

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#50** What do you recommend?

A. Continue present ART regimen**
B. Change TAF/emtricitabine to ABC/lamivudine
C. Change bictegravir to darunavir/ritonavir
D. Add darunavir/ritonavir
E. Start filgrastim (G-CSF)

3 of 3

BOARD REVIEW DAY 4

**#51** A 46-year-old man with HIV infection is seen for fever and hypotension. For the past 4 months, he has been receiving treatment for disseminated histoplasmosis.

He initially was treated with amphotericin B and is now taking itraconazole. His urine *Histoplasma* antigen is being monitored and has recently been negative. He is also receiving antiretroviral therapy according to guideline recommendations.

He has been feeling weak and tired but generally has been doing well.

Yesterday he had surgery under conscious sedation with propofol for an impacted and infected wisdom tooth. The night of surgery he developed fever and was given vancomycin and ceftriaxone by the surgical team.

1 of 4

BOARD REVIEW DAY 4

**#51** This morning he was hypotensive and experienced abdominal pain. He is now on pressors.

- His temperature is 101.8°F; pulse 122/minute, BP 84/62 mmHg.
- He has mild, diffuse abdominal tenderness but no rebound, has audible bowel sounds and is otherwise unremarkable
- His leukocyte count is 6,120 cells/µl with 72% neutrophils, 23% lymphocytes and 5% eosinophils
- His sodium is 125 mEq/L; potassium is 5.7 mEq/L; creatinine is 1.9 mg/dL; $HCO_3$ is 20 mEq/L
- Blood cultures are negative at 18 hours
- Piperacillin- tazobactam has been started for the possibility of sepsis from an oral source

2 of 4

BOARD REVIEW DAY 4

**#51** Which of the following would be the most helpful addition to his regimen to reverse his hypotension and abdominal pain?

A. Dantrolene
B. Caspofungin
C. Liposomal amphotericin B
D. Voriconazole
E. Hydrocortisone

3 of 4

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#51** **Which of the following would be the most helpful addition to his regimen to reverse his hypotension and abdominal pain?**

A. Dantrolene
B. Caspofungin
C. Liposomal amphotericin B
D. Voriconazole
E. Hydrocortisone**

4 of 4

BOARD REVIEW DAY 4

**#52** **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. The pain is significant.**



**He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States. He is HIV uninfected by recent rapid test.**

1 of 3

BOARD REVIEW DAY 4

**#52** **Which of the following diagnostic tests is most likely to yield the specific diagnosis?**

A. Serum RPR
B. Antibody to herpes simplex virus-1 and -2
C. Darkfield microscopy
D. PCR for herpes simplex virus
E. Bacterial culture

2 of 3

BOARD REVIEW DAY 4

**#52** **Which of the following diagnostic tests is most likely to yield the specific diagnosis?**

A. Serum RPR
B. Antibody to herpes simplex virus-1 and -2
C. Darkfield microscopy
D. PCR for herpes simplex virus**
E. Bacterial culture

3 of 3

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#53** A 67-year-old man is admitted with confusion, headache and fever for 1 day. He has a history of polymyalgia rheumatica for which he takes prednisone 30 mg/day and trimethoprim-sulfamethoxazole single strength tablet daily *for Pneumocystis* prophylaxis. He was hospitalized 6 months previously for *Escherichia coli* bacteremia with no source identified.

He lives in rural Georgia with his wife and 3 dogs.

On exam his temperature is 103°F. He inconsistently responds to questions with yes/no answers only. He resists passive flexion of the neck.



BOARD REVIEW DAY 4

**#53** A CBC returns with a WBC of 26 x $10^9$/L (90% segmented neutrophils, 8% lymphocytes, 2% eosinophils).

Urinalysis is bland. A lumbar puncture is performed with 977 WBC/μl (95% neutrophils), glucose of 25 mg/dL and protein of 130 mg/dL.

Blood and CSF cultures grow pan-susceptible *Enterococcus faecalis*.



BOARD REVIEW DAY 4

**#53** In addition to starting treatment with ampicillin and ceftriaxone, what additional work-up is indicated?

A. Contrasted CT scan of the abdomen and pelvis
B. Colonoscopy
C. PET scan
D. Quantitative immunoglobulin levels
E. Serology for *Strongyloides stercoralis*



BOARD REVIEW DAY 4

**#53** In addition to starting treatment with ampicillin and ceftriaxone, what additional work-up is indicated?

A. Contrasted CT scan of the abdomen and pelvis
B. Colonoscopy
C. PET scan
D. Quantitative immunoglobulin levels
E. Serology for *Strongyloides stercoralis***



**BR4 Board Review Questions - Day 4**

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#54** **A 40-year-old woman from Taiwan who was recently visiting her daughter in the US developed fever, epigastric pain, and nausea.**

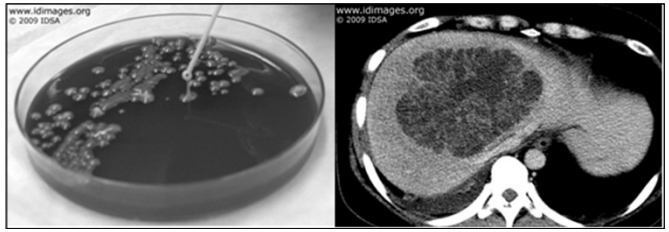
**One week later, she was brought to the emergency department because of confusion and fever. On examination, her temperature was 101°F. She had right upper quadrant abdominal tenderness.**

**An abdominal CT scan showed a 10 cm hypoattenuated liver lesion (below).**



BOARD REVIEW DAY 4

**#54** **An aspirate was performed; the culture showed mucoid colonies of an aerobic, Gram-negative rod with a positive string test. Her daughter likes to serve raw oysters and has a cat.**






BOARD REVIEW DAY 4

**#54** **Which of the following is the most likely organism?**

A. ***Vibrio parahaemolyticus***
B. ***Aeromonas* species**
C. ***Fusobacterium necrophorum***
D. ***Pasteurella multocida***
E. ***Klebsiella pneumoniae***



BOARD REVIEW DAY 4

**#54** **Which of the following is the most likely organism?**

A. ***Vibrio parahaemolyticus***
B. ***Aeromonas* species**
C. ***Fusobacterium necrophorum***
D. ***Pasteurella multocida***
E. ***Klebsiella pneumoniae*****



# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#55** A 33-year-old male who has multiple sexual partners had unprotected anal intercourse for the first time last night. This new partner mentioned after the interaction that he does have HIV infection, and he "usually" takes his drugs.

In the past, you have seen the patient every 3 months for HIV testing, and he has been HIV negative to date and has never had a sexually transmitted infection.

You perform a rapid HIV test which is negative.

The patient has no symptoms other than severe anxiety, and no new physical findings.

Routine laboratory values are normal.

1 of 3

BOARD REVIEW DAY 4

**#55** What would you recommend with regards to post exposure management and reducing risk of HIV infection?

A. No testing or therapy unless the patient has findings consistent with acute HIV infection
B. Follow the patient with monthly HIV antibody tests for 6 months but no therapy if he remains negative
C. Follow the patient with monthly HIV antigen/antibody tests but no therapy if he remains negative
D. Treatment with tenofovir alafenamide/emtricitabine for 12 weeks and periodic HIV serologic testing during and after prophylaxis
E. Treatment with bictegravir/tenofovir alafenamide/emtricitabine for 4 weeks (28 days) and periodic serologic testing and periodic HIV serologic testing during and after prophylaxis

2 of 3

BOARD REVIEW DAY 4

**#55** What would you recommend with regards to post exposure management and reducing risk of HIV infection?

A. No testing or therapy unless the patient has findings consistent with acute HIV infection
B. Follow the patient with monthly HIV antibody tests for 6 months but no therapy if he remains negative
C. Follow the patient with monthly HIV antigen/antibody tests but no therapy if he remains negative
D. Treatment with tenofovir alafenamide/emtricitabine for 12 weeks and periodic HIV serologic testing during and after prophylaxis
E. Treatment with bictegravir/tenofovir alafenamide/emtricitabine for 4 weeks (28 days) and periodic serologic testing and periodic HIV serologic testing during and after prophylaxis**

3 of 3

BOARD REVIEW DAY 4

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

She is highly sensitized (has HLA antibodies that put her at higher risk of rejection) and is thus maintained on high doses of immunosuppression. Her regimen includes belatacept, mycophenolate mofetil, and prednisone.

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

She now has a rising CMV viral load (44,000 IU/ml plasma) on treatment dose valganciclovir (900 mg twice a day).

1 of 4

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#56** She feels a bit fatigued and has some diarrhea, with no visual changes or other symptoms.

Her transplant doctors are reluctant to reduce immunosuppression further.

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



BOARD REVIEW DAY 4

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

A. High dose valacyclovir 8 grams/day
B. CMV immunoglobulin
C. High dose intravenous ganciclovir
D. Maribavir
E. Letermovir



BOARD REVIEW DAY 4

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

A. High dose valacyclovir 8 grams/day
B. CMV immunoglobulin
C. High dose intravenous ganciclovir
D. Maribavir**
E. Letermovir



BOARD REVIEW DAY 4

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

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

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



**BR4 Board Review Questions - Day 4**

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#57** **What do you recommend?**

A. Continue present ART regimen
B. Obtain integrase phenotype
C. Change bictegravir to darunavir/ritonavir
D. Add darunavir/ritonavir to current regimen
E. Double the bictegravir dose

2 of 3

BOARD REVIEW DAY 4

**#57** **What do you recommend?**

A. Continue present ART regimen
B. Obtain integrase phenotype
C. Change bictegravir to darunavir/ritonavir**
D. Add darunavir/ritonavir to current regimen
E. Double the bictegravir dose

3 of 3

BOARD REVIEW DAY 4

**#58** **A 41-year-old male with HIV presents for initial evaluation. His CD4 count is 141 cells/µl (9%), HIV viral load 111,580 copies/µL, CrCl 90 cc/min.**

**He also reports a recent history of injecting drug use with heroin, which is being treated with methadone maintenance for which he is on a stable dose.**

**The patient reports previous attempts at treatment with antiretroviral but was poorly adherent but now feels ready to resume treatment. No resistance mutations are found on HIV genotyping, and you decide to initiate TAF/FTC + DRV/r given the high barrier to resistance.**

1 of 4

BOARD REVIEW DAY 4

**#58** **The patient and his counselor at the shelter where he lives report that he is adherent to the regimen prescribed by his health care team.**

**Ten days after initiating treatment the patient returns to your office. He reports abdominal cramping, diarrhea, rhinorrhea, piloerection and irritability.**

**Here is a photo of his piloerection:**



2 of 4

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#58** **What is the most likely cause of his symptoms?**

A. IRIS
B. Enteric bacterial pathogen (*Salmonella* species, *Shigella* species, *Campylobacter* species)
C. Drug interaction
D. Darunavir toxicity
E. Influenza

3 of 4

BOARD REVIEW DAY 4

**#58** **What is the most likely cause of his symptoms?**

A. IRIS
B. Enteric bacterial pathogen (*Salmonella* species, *Shigella* species, *Campylobacter* species)
C. Drug interaction**
D. Darunavir toxicity
E. Influenza

4 of 4

BOARD REVIEW DAY 4

**#59** **A 29-year-old female developed her first bout of meningitis at age 24. Since then, she has had 3 other episodes. Each is associated with headache, stiff neck, and photophobia. Each has been treated with appropriate doses of antibiotics and resolved over several days, and all cerebrospinal fluid (CSF) cultures have been negative.**

**Her last CSF results at the time of an acute episode revealed a WBC of 230/mm$^3$ (92% lymphocytes with some large and atypical appearing cells), normal glucose, and protein of 110 mg/dL.**

1 of 4

BOARD REVIEW DAY 4

**#59** **All routine bacterial cultures and Gram stains have been negative.**

**The patient has been well otherwise but has a history of both oral and genital herpes simplex infections, and a remote history of treated syphilis.**

**She has refused permission for a human immunodeficiency virus test in the past.**

2 of 4

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#59** **This young woman's recurrent meningitis is most likely due to which of the following?**

A. Herpes simplex virus type 2
B. Varicella zoster virus
C. Cytomegalovirus
D. *Treponema pallidum*
E. Human immunodeficiency virus

3 of 4

BOARD REVIEW DAY 4

**#59** **This young woman's recurrent meningitis is most likely due to which of the following?**

A. Herpes simplex virus type 2**
B. Varicella zoster virus
C. Cytomegalovirus
D. *Treponema pallidum*
E. Human immunodeficiency virus

4 of 4

BOARD REVIEW DAY 4

**#60** **A 35-year-old patient with substance use disorder from New York City with HIV/AIDS was seen in clinic for a 1-cm slightly tender, erythematous draining skin nodule on his left thigh.**

**Pus squeezed from the lesion was negative on Gram stain but had unbranched bacilli on acid-fast smear.**

**The patient failed to keep his next clinic appointment but appeared again 8 weeks later with four more lesions on the same extremity.**

1 of 4

BOARD REVIEW DAY 4

**#60** **He had not lost weight, reported no fever, and did not seem more ill than on prior visits.**

**Acid-fast cultures grown at 35°C on Middlebrook 7H11 agar and an automated broth system from his last visit had been reported negative for mycobacteria.**

**Routine culture grew scant *Staphylococcus epidermidis*.**

2 of 4

# BR4 Board Review Questions - Day 4

*Moderator: Roy Gulick, MD*

© 2026 Infectious Disease Board Review

BOARD REVIEW DAY 4

**#60** **Which of the following is the most likely causative organism?**

A. ***Mycobacterium leprae***
B. ***Mycobacterium ulcerans***
C. ***Mycobacterium chelonae***
D. ***Mycobacterium haemophilum***
E. ***Mycobacterium malmoense***



BOARD REVIEW DAY 4

**#60** **Which of the following is the most likely causative organism?**

A. ***Mycobacterium leprae***
B. ***Mycobacterium ulcerans***
C. ***Mycobacterium chelonae***
D. ***Mycobacterium haemophilum*****
E. ***Mycobacterium malmoense***



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

© 2026 Infectious Disease Board Review

Tuesday, August 25, 2026

38

# CMV, EBV, HHV 6, and HHV 8

Camille Kotton, MD

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




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

**Camille Nelson Kotton MD, FAST, FIDSA**

Clinical Director, Transplant & Immunocompromised Host Infectious Diseases Group, Infectious Diseases Division, Massachusetts General Hospital

Associate Professor, Harvard Medical School

Prior Chair, Infectious Disease Community of Practice, American Society of Transplantation

Prior President, Infectious Disease Section; Secretary, The Transplantation Society

9/7/2026




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

| Company | Role | Details |
|---|---|---|
| Evrys | Consultant | CMV treatment in transplant |
| Merck | Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME) | Transplant infections<br>CMV antiviral trial, adjudication<br>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 |

## Human Herpesviruses Family

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

## Differential Diagnosis of Pharyngitis

Table 1. **Differential Diagnosis of Pharyngitis.***

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

* Data are from Alcaide and Bisno.[29]
† Season is applicable only in temperate climates.
‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

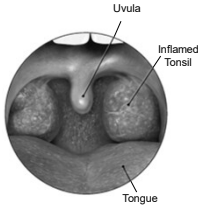
Luzuriaga K, Sullivan JL. N Engl J Med 2010;362:1993-2000



© 2026 Infectious Disease Board Review

## Features of Common Causes of Mononucleosis Syndrome

| | EBV | CMV | Toxo | HIV |
|---|---|---|---|---|
| Fever | ++++ | ++++ | ++ | ++++ |
| Myalgias / Arthralgias | ++ | +++ | + | +++ |
| Lymphadenopathy | ++++ | + | ++++ | +++ |
| Sore throat | ++++ | ++ | + | +++ |
| Exudative pharyngitis | ++++ | + | 0 | 0 |
| Headache | +++ | ++ | + | ++ |
| Rash | + | + | + | +++ |
| Splenomegaly | +++ | ++ | + | ++ |
| Hepatomegaly | + | ++ | + | 0 |
| Atypical lymphocytes (>10%) | ++++ | +++ | + | ++ |
| Elevated LFTs | ++++ | +++ | 0 | + |




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Epstein Barr Virus (EBV)

## Epstein Barr Virus: Epidemiology

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

## Epstein Barr Virus: Mononucleosis

- Transmission - saliva (due to prolonged shedding for months), sexual
- Long incubation period – 4 to 8 weeks
- Clinical – viral prodrome with fever, malaise, headache
  - Pharyngitis with tonsillar exudate
  - Symmetrical cervical adenopathy, posterior > anterior
  - Palatal petechiae, periorbital edema, and rash (maculopapular, urticarial, or petechial)
  - Splenomegaly in 15 to 65% of cases
  - Acute symptoms persist 1-2 weeks, fatigue can last for months
- Lab - > 40% lymphocytosis with atypical lymphocytes



© 2026 Infectious Disease Board Review

## Epstein Barr Virus: Mononucleosis (cont.)

- Diagnosis - serology
  - Non-specific heterophile Ab (“monospot”) sensitivity 87%, specificity 91%
  - EBV specific Ab panel
- EBV viral load/PCR - not necessary for routine mononucleosis, may be useful in transplant or other immunocompromised patients
- Therapy - supportive, no antiviral therapy, steroids for upper-airway obstruction, hemolytic anemia, and thrombocytopenia (rash with ampicillin)
- Prevention - no vaccine (Moderna mRNA vaccine phase 1 Eclipse Trial, ending 2026?)
- EBV reactivation mostly asymptomatic; can reflect extent of immunosuppression

## Complications of Primary EBV Infection/ Infectious Mononucleosis

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**General:**

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

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

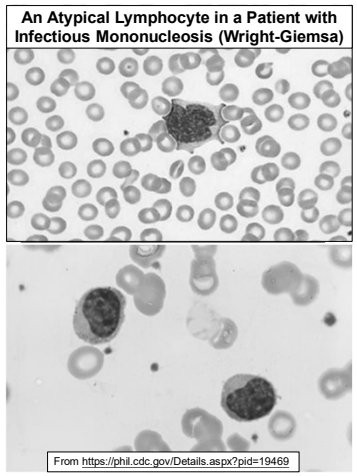
- Prolonged fatigue/malaise (>6 mo. in 10%)
- Hepatitis, rarely with fulminant hepatic failure
- Pneumonitis
- Peritonsillar abscess
- Airway obstruction from massive adenopathy

**Heme syndromes:**

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

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

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




**Atypical Lymphocytes**

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

General Features:

- Low nuclear / cytoplasmic ratio
- Indented or lobulated nuclei with nucleoli
- Cytoplasm often basophilic; can be “sky blue”, with vacuoles and granules
- Only seen on manual diff (not auto)

**38 CMV, EBV, HHV6 and HHV8**

*Speaker: Camille Kotton, MD*

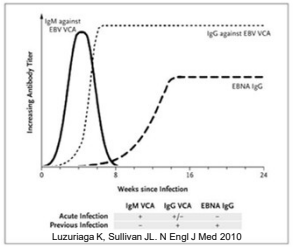
© 2026 Infectious Disease Board Review

## Non-ID Causes of *Mononucleosis Syndrome with Atypical Lymphocytosis*

- **Drug hypersensitivity syndrome**
  - Anticonvulsants such as **phenytoin, carbamazepine**
  - Antibiotics such as **isoniazid, minocycline**
- **Chronic lymphocytic leukemia (CLL), T-cell lymphomas or leukemias**
- **Autoimmune Diseases: with immune dysfunction:**
  - **Systemic Lupus Erythematosus (SLE).**
  - **Rheumatoid Arthritis (RA).**
  - **Adult-onset Still's disease.**
  - **Autoimmune Hemolytic Anemia (AIHA)**
  - **Immune Thrombocytopenia Purpura (ITP)**

## EBV Serology

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



Luzuriaga K, Sullivan JL. N Engl J Med 2010

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

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

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

Science 375, 296–301 (2022)

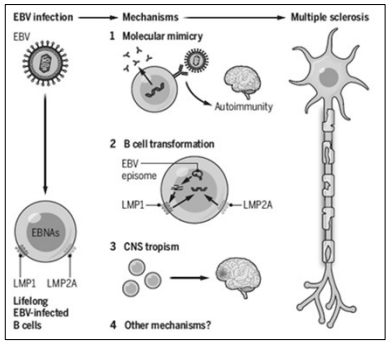
Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were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

**Proposed mechanisms:**

- Molecular mimicry
- Dysregulated EBV infection → collateral damage

**My interpretation:**

- Interesting observation
- Nothing for us/no antiviral treatments
- EBV vaccine could be helpful in the future (?)




**Model for multiple sclerosis development**

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## EBV After Organ/Stem Cell Transplantation

- High risk for EBV syndromes and proceeding to post-transplant lymphoproliferative disorder (PTLD), especially if donor seropositive/recipient seronegative (D+R-)
  - Best to monitor EBV viral load periodically for the first two years after transplant
  - If EBV viremia, reduce immune suppression whenever possible
- Low EBV viremia (<~5,000 IU/ml) may reflect immunosuppressed state
- No evidence that any currently available antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

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

Preiksaitis et al, The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring, Pedia Transplant 2024

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## Question #1

- A 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.
- Her heterophile antibody test (Monospot) is **negative**. In addition to other tests, you order EBV-specific serology.

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

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


## Question #1

- A 14-year-old female presents to your office with sore throat, fever, and malaise, with lymphadenopathy and pharyngitis on physical exam.
- Her heterophile antibody test (Monospot) is **negative**. In addition to other tests, you order EBV-specific serology.

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

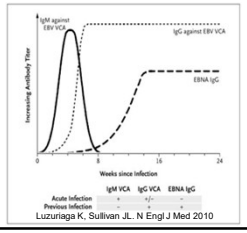

| Response | VCA IgM | VCA IgG | EBNA IgG | EA IgG |
|---|---|---|---|---|
| A | + | + | + | + |
| **B** | **+** | **+** | **-** | **+** |
| C | - | + | + | + |
| D | - | - | + | - |


## Question #1


The correct answer is B: VCA IgM positive, VCA IgG positive, EBNA IgG negative, EA IgG+.

Antibodies directed against the **viral capsid antigen (VCA), both IgM and IgG**, and **EA IgG**, are usually detectable at the time of symptom onset. VCA IgG persists for life, while VCA IgM disappears after about a year. Epstein-Barr nuclear antigen (EBNA) IgG does not appear for several weeks after symptom onset and also persists for life.


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


Luzuriaga K, Sullivan JL. N Engl J Med 2010

## Cytomegalovirus (CMV)




© 2026 Infectious Disease Board Review

## Epidemiology of CMV Infection

- Age-specific peaks in incidence:
  - Children in USA: 10-15% infected before age 5
  - Young adults at onset of sexual activity
  - ~50% adults are CMV IgG+ (NHANES, Bate et al, Clin Infect Dis 2010)
  - In low-income regions, CMV seroprevalence approaches 100%
- Transplant:
  - Organ: highest risk is donor seropositive, recipient seronegative (D+R-)
  - Stem cell: highest risk is D-R+ (opposite)
  - Superinfection can occur (organ transplant D+R+ higher risk than D-R+)
- Immunocompromised hosts
  - Seen with inflammatory bowel disease; might drive pathogenesis?
  - Can see atypical syndromes – worth checking

## Transmission & Pathogenesis of CMV

- Beta herpesvirus
- Infection transmitted via:
  - Body fluids (urine, semen, cervical secretions, saliva, breast milk)
  - Transplanted tissue (blood, organs, stem cell transplant)
    - Reduced with routine use of blood filtered/WBC-depleted
- Primary infection usually asymptomatic/subclinical
  - Mononucleosis syndrome in <10%
- Viral replication in WBCs, epithelial cells (kidney, salivary glands, etc.)
- Following primary infection, prolonged viremia (weeks) and viruria (months) persist despite humoral and cellular immune responses.
  - Ongoing shed is important factor in transmission
- No vaccine available; some under development (Moderna mRNA CMV vaccine failed, 2025)

## CMV Mononucleosis Syndrome

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

## CMV Congenital Infection

- Leading cause of nonhereditary sensorineural hearing loss in USA
  - Can cause other long-term neurodevelopmental issues, including cerebral palsy, intellectual disability, seizures, vision impairment
- Congenital CMV 0.6% prevalence in high income countries
  - 40,000 children/year in USA
- Primary maternal CMV infection - 30-40% risk of congenital infection
  - Having children in daycare is major risk
- Reactivation maternal CMV infection - 0.9-1.5% risk of congenital infection
- Newborn screening under evaluation, sensitivity of dried blood spots for detecting congenital CMV infection is 73-78%
- *Treatment controversial – not for boards*


© 2026 Infectious Disease Board Review

## Cytomegalovirus: The Troll of Transplantation

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

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



Special Feature

Transplantation ■ xxx 2025

**The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation**

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[9]; on behalf of The Transplantation Society International CMV Consensus Group*

*Lancet Infect Dis* 2025

**Recommendations from the 10th European Conference on Infections in Leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies**

*Per Ljungman, Sophie Alain, Roy F Chemaly, Hermann Einsele, Federica Galaverna, Hans H Hirsch, Alicja Sadowska-Klasa, David Navarro, Jan Styczynski, Rafael de la Camara*

## CMV Infection After Organ/Stem Cell Transplant: A Spectrum Of Disease

**Direct Effects**

**Asymptomatic Viremia**

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

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

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

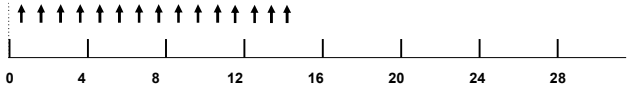
## PREVENTION: Prophylaxis vs. Preemptive Therapy

**Prophylaxis** period (typically 3–6 months) after transplantation

**Antiviral prophylaxis**

**Valganciclovir after solid organ transplant**
**Letermovir after stem cell/D+R- kidney transplant**

**Preemptive monitoring** period (once weekly for 12–16 weeks); If CMV is detected (PCR or pp65 Ag), treat until CMV is cleared




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

**38 CMV, EBV, HHV6 and HHV8**

*Speaker: Camille Kotton, MD*

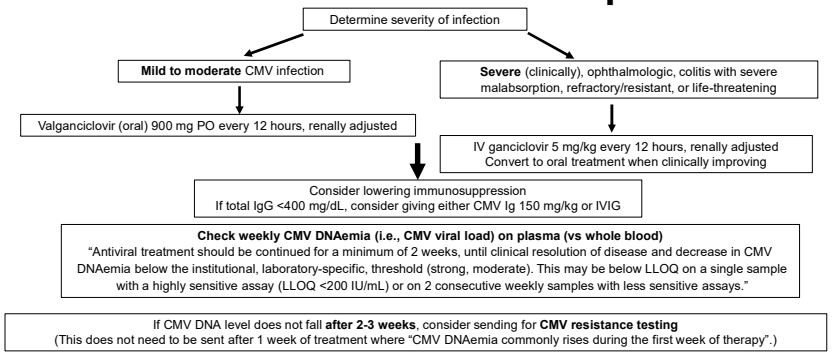
© 2026 Infectious Disease Board Review

# CMV Diagnostics

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# Treatment of CMV After Transplant




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Ig: immunoglobulin; IV: intravenous; PO: by mouth; LLOQ, the lower limit of quantification
Modified from Kotton CN, et al. *Transplantation*. 2025. doi:10.1097/TP.0000000000005374.

# CMV Genotyping for Drug Resistance

**Sanger sequencing** (classic): Can detect resistant subpopulations down to 20%-30%

**Next-generation sequencing**: Can detect resistant subpopulations as low as 10% of the total viral population

Prior to resistance testing, or for those of you without access to CMV genotyping, follow the algorithm with presumptions as to best choices

To ensure a high-quality sequencing result, the current CMV DNAemia must be >2.6 log IU/mL (>400 IU/mL, best if >1000 IU/mL) (better results with higher DNAemia)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# Ensure Correct CMV Resistance Testing Ordered

| Detects Resistance to: | UL97 Phosphotrans-ferase | UL54 Polymerase | UL27 | UL56 Terminase |
|---|---|---|---|---|
| Maribavir, Letermovir, Ganciclovir, Foscarnet, Cidofovir | x | | | |
| Maribavir, Ganciclovir, Foscarnet, Cidofovir | | x | | |
| Maribavir | | | x | |
| Letermovir | | | | x |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**38 CMV, EBV, HHV6 and HHV8**

*Speaker: Camille Kotton, MD*

© 2026 Infectious Disease Board Review

## What is the updated definition of resistant/refractory CMV (for clinical trials, also applies clinically)?

**Resistant CMV infection**: Refractory CMV plus the presence of a ***known viral genetic mutation(s)*** that decreases the susceptibility to ≥1 anti-CMV medications.

***Refractory CMV infection***: Defined as CMV viremia (DNAemia or antigenemia) that **increases (i.e., >1 $log_{10}$ increase in CMV DNA levels in the same blood compartment from the peak viral load as measured in the same laboratory and/or with the same commercial assay) OR persists** (≤1 $log_{10}$ increase or decrease in CMV DNA levels) **after ≥2 weeks of appropriate antiviral therapy**

***Refractory CMV end-organ disease***: Defined by a worsening in signs and symptoms or progression to end-organ disease (for a patient not previously diagnosed with CMV end-organ disease) OR lack of improvement in signs and symptoms after **≥2 weeks of appropriately dosed antiviral therapy**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Ljungman P, et al. *Clin Infect Dis.* 2024;79:787-794.

## Maribavir: Current State of Regulatory Approval

- Approved by Federal Drug & Food Administration (FDA) in December 2021 (≥ 12 years old) and European Medicines Agency in September 2022 (adults) for **treatment of resistant/refractory CMV disease after SOT/HSCT**
- **Not yet approved for treatment outside of resistant/refractory CMV disease**
  - "A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the **Treatment of Asymptomatic Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients**", ClinicalTrials.gov: NCT02927067 → did not reach non-inferiority endpoint
- Unlikely to move forward as prophylaxis in the near future
  - Prior failure in stem cell and liver transplant (likely due to doses used)
- Not for use with **retinitis or CNS disease**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Clinically significant drug interactions with maribavir

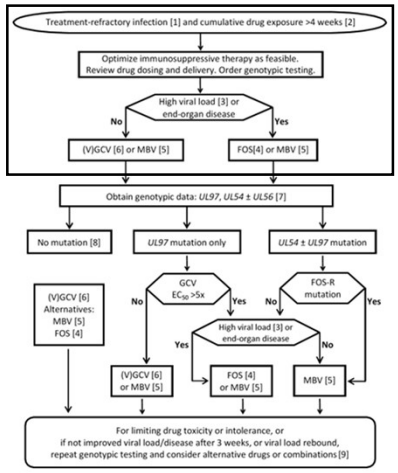
| Cytochrome-P450 (CYP)/P-glycoprotein | Concomitant medication | Clinical implication of interaction | Clinical management of interaction |
|---|---|---|---|
| **CYP-3A4 substrate/ P-glycoprotein substrate** | Cyclosporine | Increase cyclosporine concentration | Patients concomitantly receiving maribavir and CYP-3A4/ P-glycoprotein substrates (cyclosporine, everolimus, tacrolimus, sirolimus) should have plasma levels monitored starting at initiation through discontinuation of maribavir. |
| | Everolimus | Increase everolimus concentration | |
| | Tacrolimus | Increase tacrolimus $C_{max}$ 38% and AUC 51% | |
| | Sirolimus | Increase sirolimus concentration | |
| | Digoxin | Increase digoxin concentrations | Digoxin plasma concentrations should be monitored starting at initiation through discontinuation of maribavir. |
| | Rosuvastatin | Increase rosuvastatin concentrations | Monitor for myopathy and rhabdomyolysis |
| **CYP-3A4/ P-glycoprotein strong-moderate inhibitor** | Diltiazem | Increase maribavir $C_{max}$ 6% and AUC 9% | Can consider co-administering maribavir with strong CYP3A4 inhibitors without dose adjustment, based on lack of toxicities associated with doses up to 1200mg twice daily in studies and lack of 3-fold increase in AUC with strong-moderate CYP-3A4 inhibitors. |
| | Erythromycin | Increase maribavir $C_{max}$ 26% and AUC 44% | |
| | Ketoconazole | Increase maribavir $C_{max}$ 17% and AUC 54% | |
| | Ritonavir | Increase maribavir $C_{max}$ 37% and AUC 63% | |
| **CYP3A4/P P-glycoprotein strong-moderate inducer** | Carbamazepine | Decrease maribavir $C_{max}$ 23% and AUC 29% | Consider increasing maribavir doses to 800-1200 mg twice daily |
| | Efavirenz | Decrease maribavir $C_{max}$ 25% and AUC 42% | Consider increasing maribavir doses to 1200-1600 mg twice daily |
| | Phenobarbital | Decrease maribavir $C_{max}$ 27% and AUC 39% | Consider increasing maribavir doses to 800-1200 mg twice daily |
| | Phenytoin | Decrease maribavir $C_{max}$ 31% and AUC 42% | Consider increasing maribavir doses to 1200mg twice daily |
| | Rifampin | Decrease maribavir $C_{max}$ AUC 61% | Co-administration should be avoided, and alternative antimicrobial or antituberculosis therapy should be considered if alternative CMV agents cannot be used. |
| **CYP2C19 substrate** | Voriconazole | No effect | Maribavir and voriconazole may be co-administered without dose adjustment. Unknown if interactions with posaconazole, itraconazole, and isavuconazole, exist, but unlikely based on voriconazole data. |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi RG & Kotton CN, Evaluating the Safety of Maribavir for the Treatment of CMV, Therapeutics and Clinical Risk Management 2022:18 223–232

## Flowchart for Management of Suspected Drug-Resistant CMV Infection: CMV Guidelines

- FOS is suggested for high viral loads in clinically unwell patients. High viral load: ≥50 000 (4.7 log10) IU/mL (plasma). MBV works better with lower viral loads, see the text
- Avoid MBV for CNS disease or retinitis




Kotton CN, Kumar D, Oriol M, et al. Transplantation. 2025. doi:10.1097/TP.0000000000005374

CNS: central nervous system; FOS: foscarnet; GCV: ganciclovir; MBV: maribavir.

For educational purposes only.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

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**
- **Leukopenia or neutropenia** by week 28 lower w/ letermovir vs valganciclovir (26% vs 64%; P < .001)
- 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 dose adjusted to renal function, details N/A—could explain neutropenia & breakthrough infections
- IMPACT trial (Humar A et al, 2010) comparing 100 vs 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

MERCK

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

*previously approved for stem cell transplant prophylaxis

**Important Drug Interactions**
Tacrolimus
Cyclosporine
Azoles



**US$277** letermovir 480 mg/d vs **US$5** valganciclovir 900 mg/d per goodrx.com w/ coupon (April 2026)

**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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Pseudotumor presentation of CMV disease: Diagnostic dilemma and association with immunomodulating therapy

Olivia C. Smibert[1,2] | Cody C. Allison[3] | Marcel Doerflinger[3] | Marc Pellegrini[3] | Danny Rischin[4] | Alesha Thai[4] | Monica A. Slavin[2,5] | Camille N. Kotton[1]

"Cytomegalo-tumor"



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



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

Transplant Infect Dis. 2020;00:e13533. https://doi.org/10.1111/tid.13533

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# Question #2

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

### What do you recommend?

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

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

C. Call a transplant ID colleague for guidance



© 2026 Infectious Disease Board Review

## Question #2

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

### What do you recommend?

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

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

C. Call a transplant ID colleague for guidance

## Question #2

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

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

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

## Human Herpesvirus Type 6 (HHV-6)

## Human Herpesvirus Type 6

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## Exanthem subitum (Roseola, Sixth disease)





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

## Human Herpesvirus Type 6: Normal Hosts

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

**because it was the sixth common childhood rash that scientists named:*
*measles, scarlet fever, rubella, Dukes' disease (now same as scarlet fever), and erythema infectiosum (parvovirus B19)*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - **Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days**
    - 1% of those with HHV-6 viremia
    - Acute memory loss, altered mental status, and seizures; fever is rare
    - Bone marrow suppression (maybe also GVHD?)
  - Rare after CAR-T (reactivation 6%, mostly low level)
- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
    - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
    - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-30,000 copies/ml
    - Encephalitis – Mild CSF lymphocytic pleocytosis, temporal abnormalities shown on EEG, and MRI hyperintense lesions in the limbic system
- Therapy
  - Ganciclovir and/or foscarnet x ≥ 3 weeks; decide based on toxicities; cidofovir last choice
  - Treat if encephalitis; not all need treatment, not if just low-level HHV-6+ in blood/CSF
  - Reduce immunosuppression if possible; do not use steroids

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## The BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Distinguishing bacterial from viral meningitis based on clinical presentation alone is challenging.
Getting fast, pathogen-specific answers can help save lives and guide appropriate therapy.

*Make sure that the pathogen you detect fits the clinical scenario*

https://www.biofiredx.com/products/the-filmarray-panels/filmarrayme/

### THE BIOFIRE MENINGITIS/ENCEPHALITIS PANEL MENU

*Overall 94.2% Sensitivity and 99.8% Specificity[1]*
*Sample Type: Cerebrospinal Fluid (CSF) collected by lumbar puncture*

**BACTERIA:**

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

**YEAST:**

- *Cryptococcus (C. neoformans/C. gattii)*

**VIRUSES:**

- Cytomegalovirus (CMV)
- Enterovirus (EV)
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus (HPeV)
- Varicella zoster virus (VZV)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## Human Herpes Virus Type (HHV-8)

## Human Herpesvirus Type 8

- Gamma herpesvirus, discovered 1994
- Kaposi sarcoma-associated herpesvirus (KSHV)
- HHV-8 seroprevalence in the US (highly variable internationally):
  - Blood donor populations: 1-5%
  - MSM: 8-25%
  - HIV-positive MSM: 30-77%
  - HIV-positive with KS: 90%
- Route of transmission unknown – sexual, saliva?
  - Transmission via SOT documented (rare)
- 1° infection usually asymptomatic, some with febrile rash syndrome

## HHV-8 Associated Diseases

- **Kaposi sarcoma:** 4 types
  - **Classic:** indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - **Endemic:** all parts of equatorial Africa, Mediterranean, affecting children & adults, can be more aggressive than classic
  - **Transplant-associated:** more often donor-derived (D+R-), can be reactivation
  - **Epidemic/AIDS-related:** KS = most common tumor in people with HIV; AIDS-defining illness
- **Primary effusion lymphoma (body cavity-based lymphoma)**
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleura, pericardium, or peritoneum
- **Castleman's disease (HIV+ and HIV-)**
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- **KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+ and organ transplant recipients**[1]
  - Fever, pancytopenia, dysregulated inflammatory response, high IL-6, IL-10, HHV-8 VL
  - Mimics sepsis and other viral infections. High mortality rate

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

[1]Mularoni A et al, AJT 2025

## HHV-8 Diagnosis and Treatment

- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman's disease, etc
    - HHV-8 immunohistochemistry
- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi's sarcoma treated as a cancer
  - KSHV Inflammatory Cytokine Syndrome (KICS) = foscarnet + rituximab
    - Rituximab: wider blockade of the cytokine cascade through the potential eradication of HHV-8-infected CD20. B cells; reducing the reservoir → limiting viral proliferation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

U.S. Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 75 / No. 8 March 5, 2026

## Kaposi Sarcoma–Associated Herpesvirus Infection and Complications Among Solid Organ Transplant Recipients — United States, January 2021–September 2025

Ian Kracalik, PhD[1]; Pallavi Annambhotla, DrPH[1]; David W. McCormick, MD[1]; Andrew I. Geller, MD[1]; Kelsey McDavid, MPH[1]; Isabel Griffin, PhD[1]; Raymond Lynch, MD[2]; Brianna Doby, MPH[2]; Yoichiro Natori, MD[3]; Sofya Tokman, MD[4]; Christine M. Durand, MD[5]; Camille N. Kotton, MD[6]; Emily Blumberg, MD[7]; Ricardo M. La Hoz, MD[8]; Lauri A. Hicks, DO[1]; Stephanie M. Pouch, MD[9]; Sridhar V. Basavaraju, MD[1]; Donor-Derived KSHV Investigation Group

"During January 2021–September 2025, after transplantation of 185 organs into 153 recipients, 46 deceased donors were identified whose transplanted organs were suspected of having transmitted KSHV, approximately five times the number of such donors (nine) reported during 2016–2020. As of February 2026, a post-transplantation KSHV infection has been identified among 74/153 (48%)."

## Antiviral Prophylaxis & Treatment Agents

*acyclovir/valacyclovir/famciclovir and letermovir *for prophylaxis only*

**foscarnet, cidofovir, maribavir not usually used for prophylaxis

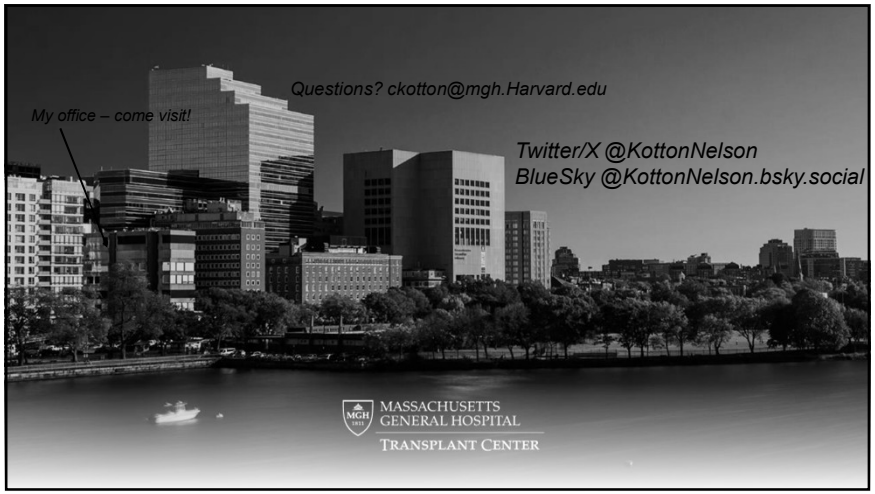
| Antiviral agent | CMV | EBV | HHV-6 | HHV-8 | HSV | Varicella | BK | Adeno-virus |
|---|---|---|---|---|---|---|---|---|
| **Commercially available** | | | | | | | | |
| acyclovir/valacyclovir/famciclovir* | high dose +/- | | | | x | x | | |
| ganciclovir IV/valganciclovir PO | x | | x | +/- | x | x | | |
| foscarnet** | x | | x | +/- | x | x | | |
| cidofovir** | x | | x | +/- | x | x | poor | +/- IC50 |
| letermovir (prophylaxis only) | **x** | | | | | | | |
| maribavir (treatment only) | **x** | *in vitro* | | | | | | |
| **Novel/investigational antiviral agents (SOT)** | | | | | | | | |
| *brincidofovir (not available)* | *x* | *x* | | | *x* | *x* | *x* | *x* |
| *pritelivir (phase III)* | | | | | *x* | | | |

Modified from Kotton CN, Updates on antiviral drugs for cytomegalovirus prevention and treatment, Curr Opin Organ Transplant 2019, 24:469–475

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

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




**38 CMV, EBV, HHV6 and HHV8**

*Speaker: Camille Kotton, MD*

© 2026 Infectious Disease Board Review

# Differential Diagnosis of Pharyngitis

Table 1. Differential Diagnosis of Pharyngitis.*

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

* Data are from Alcaide and Bisno.[29]
† Season is applicable only in temperate climates.
‡ Numbers in parentheses indicate the approximate percentage of mononucleosis cases due to the given pathogen.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

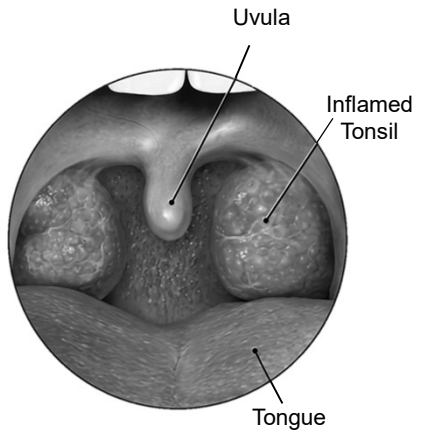
Luzuriaga K, Sullivan JL. N Engl J Med 2010;362:1993-2000



© 2026 Infectious Disease Board Review

# Features of Common Causes of Mononucleosis Syndrome

| | EBV | CMV | Toxo | HIV |
|---|---|---|---|---|
| Fever | ++++ | ++++ | ++ | ++++ |
| Myalgias / Arthralgias | ++ | +++ | + | +++ |
| Lymphadenopathy | ++++ | + | ++++ | +++ |
| Sore throat | ++++ | ++ | + | +++ |
| Exudative pharyngitis | ++++ | + | 0 | 0 |
| Headache | +++ | ++ | + | ++ |
| Rash | + | + | + | +++ |
| Splenomegaly | +++ | ++ | + | ++ |
| Hepatomegaly | + | ++ | + | 0 |
| Atypical lymphocytes (>10%) | ++++ | +++ | + | ++ |
| Elevated LFTs | ++++ | +++ | 0 | + |




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Complications of Primary EBV Infection/ Infectious Mononucleosis

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## General:

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

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

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

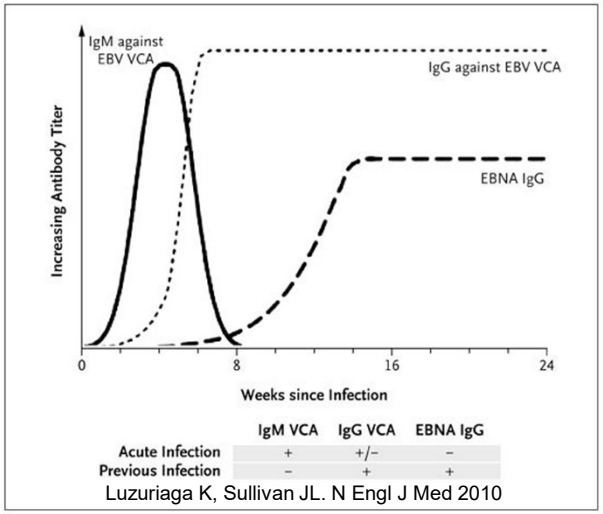
## Heme syndromes:

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


© 2026 Infectious Disease Board Review

# EBV Serology

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




| | IgM VCA | IgG VCA | EBNA IgG |
|---|---|---|---|
| Acute Infection | + | +/− | − |
| Previous Infection | − | + | + |

Luzuriaga K, Sullivan JL. N Engl J Med 2010

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



© 2026 Infectious Disease Board Review

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

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

Science 375, 296–301 (2022)

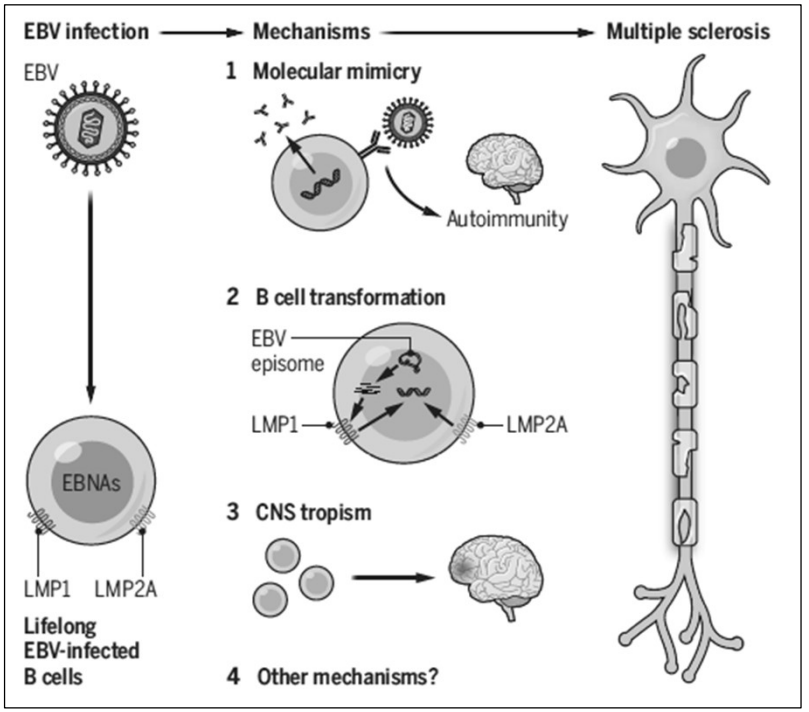
Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were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

**Proposed mechanisms:**

- Molecular mimicry
- Dysregulated EBV infection → collateral damage

**My interpretation:**

- Interesting observation
- Nothing for us/no antiviral treatments
- EBV vaccine could be helpful in the future (?)




**Model for multiple sclerosis development**

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# EBV After Organ/Stem Cell Transplantation

- High risk for EBV syndromes and proceeding to post-transplant lymphoproliferative disorder (PTLD), especially if donor seropositive/recipient seronegative (D+R-)
  - Best to monitor EBV viral load periodically for the first two years after transplant
  - If EBV viremia, reduce immune suppression whenever possible
- Low EBV viremia (<~5,000 IU/ml) may reflect immunosuppressed state
- No evidence that any currently available antiviral therapy is helpful
  - Valganciclovir only works in lytic phase (small %)
- WHO pathology classification of a tissue biopsy remains the gold standard for PTLD diagnosis
- PTLD treatment may include (in order): reduction of immunosuppression, rituximab, and cytotoxic chemotherapy

Allen and Preiksaitis, Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, Clin Trans 2019
Preiksaitis et al, The IPTA Nashville Consensus Conference on Post-Transplant lymphoproliferative disorders after solid organ transplantation in children: III - Consensus guidelines for Epstein-Barr virus load and other biomarker monitoring, Pedia Transplant 2024

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

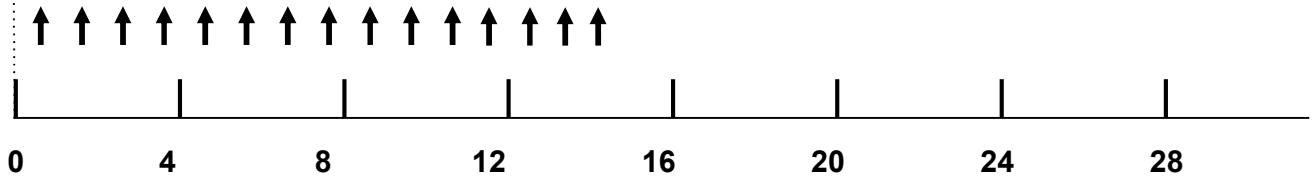
# PREVENTION:
# Prophylaxis vs. Preemptive Therapy

**Prophylaxis** period (typically 3–6 months) after transplantation

**Antiviral prophylaxis**

**Valganciclovir after solid organ transplant**
**Letermovir after stem cell/D+R- kidney transplant**

**Preemptive monitoring** period (once weekly for 12–16 weeks);
If CMV is detected (PCR or pp65 Ag), treat until CMV is cleared




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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# CMV Diagnostics

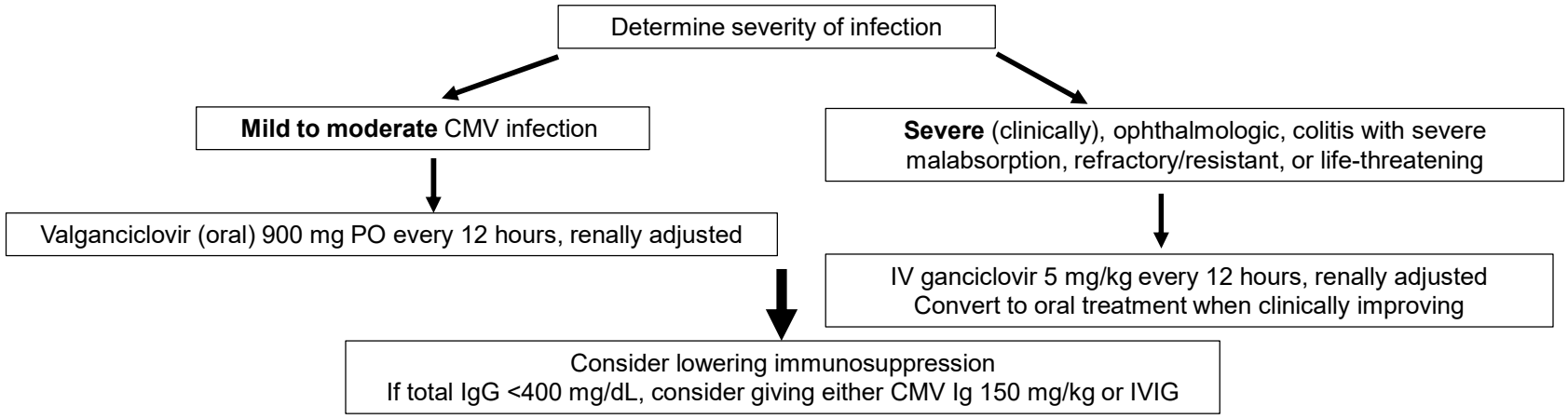
- Serology
  - To diagnose acute infection in normal host, detect IgM or IgM-->IgG seroconversion
  - CMV IgG establishes donor/recipient serostatus/risk in transplantation (no IgM)
  - Serology has no role in diagnosis of acute infection in transplant setting
- Molecular diagnostics – for immunocompromised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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Treatment of CMV After Transplant




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Ig: immunoglobulin; IV: intravenous; PO: by mouth; LLOQ, the lower limit of quantification
Modified from Kotton CN, et al. *Transplantation*. 2025. doi:10.1097/TP.0000000000005374.



© 2026 Infectious Disease Board Review

# CMV Genotyping for Drug Resistance

**Sanger sequencing** (classic): Can detect resistant subpopulations down to 20%-30%

**Next-generation sequencing**: Can detect resistant subpopulations as low as 10% of the total viral population

Prior to resistance testing, or for those of you without access to CMV genotyping, follow the algorithm with presumptions as to best choices

To ensure a high-quality sequencing result, the current CMV DNAemia must be >2.6 log IU/mL (>400 IU/mL, best if >1000 IU/mL) (better results with higher DNAemia)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Ensure Correct CMV Resistance Testing Ordered

| Detects Resistance to: | UL97 Phosphotrans-ferase | UL54 Polymerase | UL27 | UL56 Terminase |
|---|---|---|---|---|
| Maribavir, Letermovir, Ganciclovir, Foscarnet, Cidofovir | x | | | |
| Maribavir, Ganciclovir, Foscarnet, Cidofovir | | x | | |
| Maribavir | | | x | |
| Letermovir | | | | x |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# What is the updated definition of resistant/refractory CMV (for clinical trials, also applies clinically)?

**Resistant CMV infection**: Refractory CMV plus the presence of a ***known viral genetic mutation(s)*** that decreases the susceptibility to ≥1 anti-CMV medications.

***Refractory CMV infection***: Defined as CMV viremia (DNAemia or antigenemia) that **increases (i.e., >1 $\log_{10}$ increase in CMV DNA levels in the same blood compartment from the peak viral load as measured in the same laboratory and/or with the same commercial assay) OR persists** (≤1 $\log_{10}$ increase or decrease in CMV DNA levels) **after ≥2 weeks of appropriate antiviral therapy**

***Refractory CMV end-organ disease***: Defined by a worsening in signs and symptoms or progression to end-organ disease (for a patient not previously diagnosed with CMV end-organ disease) OR lack of improvement in signs and symptoms after **≥2 weeks of appropriately dosed antiviral therapy**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Ljungman P, et al. *Clin Infect Dis*. 2024;79:787-794.



© 2026 Infectious Disease Board Review

# Maribavir: Current State of Regulatory Approval

- Approved by Federal Drug & Food Administration (FDA) in December 2021 (≥ 12 years old) and European Medicines Agency in September 2022 (adults) for **treatment of resistant/refractory CMV disease after SOT/HSCT**
- **Not yet approved for treatment outside of resistant/refractory CMV disease**
  - "A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the **Treatment of Asymptomatic Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients**", ClinicalTrials.gov: NCT02927067 → did not reach non-inferiority endpoint
- Unlikely to move forward as prophylaxis in the near future
  - Prior failure in stem cell and liver transplant (likely due to doses used)
- Not for use with **retinitis or CNS disease**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Clinically significant drug interactions with maribavir

| Cytochrome-P450 (CYP)/P-glycoprotein | Concomitant medication | Clinical implication of interaction | Clinical management of interaction |
|---|---|---|---|
| **CYP-3A4 substrate/ P-glycoprotein substrate** | Cyclosporine | Increase cyclosporine concentration | Patients concomitantly receiving maribavir and CYP-3A4/ P-glycoprotein substrates (cyclosporine, everolimus, tacrolimus, sirolimus) should have plasma levels monitored starting at initiation through discontinuation of maribavir. |
| | Everolimus | Increase everolimus concentration | |
| | Tacrolimus | Increase tacrolimus $C_{max}$ 38% and AUC 51% | |
| | Sirolimus | Increase sirolimus concentration | |
| | Digoxin | Increase digoxin concentrations | Digoxin plasma concentrations should be monitored starting at initiation through discontinuation of maribavir. |
| | Rosuvastatin | Increase rosuvastatin concentrations | Monitor for myopathy and rhabdomyolysis |
| **CYP-3A4/ P-glycoprotein strong-moderate inhibitor** | Diltiazem | Increase maribavir $C_{max}$ 6% and AUC 9% | Can consider co-administering maribavir with strong CYP3A4 inhibitors without dose adjustment, based on lack of toxicities associated with doses up to 1200mg twice daily in studies and lack of 3-fold increase in AUC with strong-moderate CYP-3A4 inhibitors. |
| | Erythromycin | Increase maribavir $C_{max}$ 26% and AUC 44% | |
| | Ketoconazole | Increase maribavir $C_{max}$ 17% and AUC 54% | |
| | Ritonavir | Increase maribavir $C_{max}$ 37% and AUC 63% | |
| **CYP3A4/P P-glycoprotein strong-moderate inducer** | Carbamazepine | Decrease maribavir $C_{max}$ 23% and AUC 29% | Consider increasing maribavir doses to 800-1200 mg twice daily |
| | Efavirenz | Decrease maribavir $C_{max}$ 25% and AUC 42% | Consider increasing maribavir doses to 1200-1600 mg twice daily |
| | Phenobarbital | Decrease maribavir $C_{max}$ 27% and AUC 39% | Consider increasing maribavir doses to 800-1200 mg twice daily |
| | Phenytoin | Decrease maribavir $C_{max}$ 31% and AUC 42% | Consider increasing maribavir doses to 1200mg twice daily |
| | Rifampin | Decrease maribavir $C_{max}$ AUC 61% | Co-administration should be avoided, and alternative antimicrobial or antituberculosis therapy should be considered if alternative CMV agents cannot be used. |
| **CYP2C19 substrate** | Voriconazole | No effect | Maribavir and voriconazole may be co-administered without dose adjustment. Unknown if interactions with posaconazole, itraconazole, and isavuconazole, exist, but unlikely based on voriconazole data. |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi RG & Kotton CN, Evaluating the Safety of Maribavir for the Treatment of CMV, Therapeutics and Clinical Risk Management 2022:18 223–232

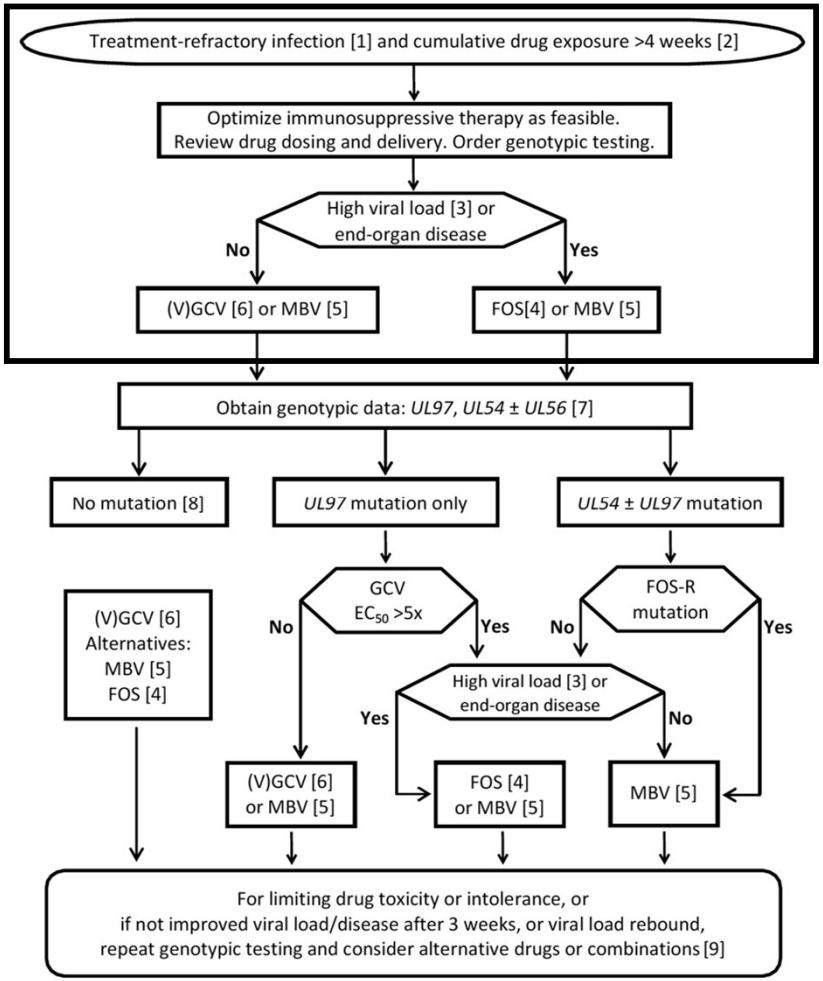


© 2026 Infectious Disease Board Review

# Flowchart for Management of Suspected Drug-Resistant CMV Infection: CMV Guidelines

- FOS is suggested for high viral loads in clinically unwell patients. High viral load: ≥50 000 (4.7 log10) IU/mL (plasma). MBV works better with lower viral loads, see the text
- Avoid MBV for CNS disease or retinitis

Kotton CN, Kumar D, Oriol M, et al. Transplantation. 2025.
doi:10.1097/TP.0000000000005374
CNS: central nervous system; FOS: foscarnet; GCV: ganciclovir; MBV: maribavir.
For educational purposes only.




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

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**
- **Leukopenia or neutropenia** by week 28 lower w/ letermovir vs valganciclovir (26% vs 64%; P < .001)
- 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 dose adjusted to renal function, details N/A—could explain neutropenia & breakthrough infections
- IMPACT trial (Humar A et al, 2010) comparing 100 vs 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

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

*previously approved for stem cell transplant prophylaxis

**Important Drug Interactions**
Tacrolimus
Cyclosporine
Azoles



**US$277** letermovir 480 mg/d vs **US$5** valganciclovir 900 mg/d per goodrx.com w/ coupon (April 2026)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**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)



© 2026 Infectious Disease Board Review

## Pseudotumor presentation of CMV disease: Diagnostic dilemma and association with immunomodulating therapy

Olivia C. Smibert[1,2] | Cody C. Allison[3] | Marcel Doerflinger[3] | Marc Pellegrini[3]
Danny Rischin[4] | Alesha Thai[4] | Monica A. Slavin[2,5] | Camille N. Kotton[1]

"Cytomegalo-tumor"



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

*Transpl Infect Dis.* 2020;00:e13531.
https://doi.org/10.1111/tid.13531



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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Human Herpesvirus Type 6

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Human Herpesvirus Type 6: Normal Hosts

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

**because it was the sixth common childhood rash that scientists named:*
*measles, scarlet fever, rubella, Dukes' disease (now same as scarlet fever), and erythema infectiosum (parvovirus B19)*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# HHV-6: Immunocompromised Hosts

- Associated syndromes
  - Reactivation disease in transplant patients
  - **Encephalitis – mostly allogeneic HCT recipients (1-3%), often in first 60 days**
    - 1% of those with HHV-6 viremia
    - Acute memory loss, altered mental status, and seizures; fever is rare
    - Bone marrow suppression (maybe also GVHD?)
  - Rare after CAR-T (reactivation 6%, mostly low level)
- Diagnosis
  - PCR from plasma (cell free), CSF, tissue
    - High prevalence of viral DNA in peripheral blood mononuclear cells limits the use of PCR to discriminate between latency and active infection, chromosomal integration can be confusing
    - CSF typically normal or only mildly abnormal, slightly elevated WBC and protein, HHV-6 PCR 15,000-30,000 copies/ml
    - Encephalitis – Mild CSF lymphocytic pleocytosis, temporal abnormalities shown on EEG, and MRI hyperintense lesions in the limbic system
- Therapy
  - Ganciclovir and/or foscarnet x ≥ 3 weeks; decide based on toxicities; cidofovir last choice
  - Treat if encephalitis;  not all need treatment, not if just low-level HHV-6+ in blood/CSF
  - Reduce immunosuppression if possible; do not use steroids

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# The BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel

Distinguishing bacterial from viral meningitis based on clinical presentation alone is challenging. Getting fast, pathogen-specific answers can help save lives and guide appropriate therapy.

*Make sure that the pathogen you detect fits the clinical scenario*

https://www.biofiredx.com/products/the-filmarray-panels/filmarrayme/

## THE BIOFIRE MENINGITIS/ENCEPHALITIS PANEL MENU

*Overall 94.2% Sensitivity and 99.8% Specificity[1]*
*Sample Type: Cerebrospinal Fluid (CSF) collected by lumbar puncture*

**BACTERIA:**

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

**VIRUSES:**

- Cytomegalovirus (CMV)
- Enterovirus (EV)
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus (HPeV)
- Varicella zoster virus (VZV)

**YEAST:**

- *Cryptococcus (C. neoformans/C. gattii)*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# HHV-8 Associated Diseases

- **Kaposi sarcoma:** 4 types
  - **Classic:** indolent cutaneous proliferative disease, mainly affecting the lower extremities of elderly men of Mediterranean and Ashkenazi Jewish origin
  - **Endemic:** all parts of equatorial Africa, Mediterranean, affecting children & adults, can be more aggressive than classic
  - **Transplant-associated:** more often donor-derived (D+R-), can be reactivation
  - **Epidemic/AIDS-related:** KS = most common tumor in people with HIV; AIDS-defining illness
- **Primary effusion lymphoma (body cavity-based lymphoma)**
  - Non-Hodgkin B-cell lymphoma, usually in HIV+. Involves pleura, pericardium, or peritoneum
- **Castleman's disease (HIV+ and HIV-)**
  - Unicentric or Multicentric; hyaline vascular or plasma cell variants – all HHV-8 related. Fever, hepatomegaly, splenomegaly, massive lymphadenopathy
- **KSHV Inflammatory Cytokine Syndrome (KICS) in HIV+ and organ transplant recipients[1]**
  - Fever, pancytopenia, dysregulated inflammatory response, high IL-6, IL-10, HHV-8 VL
  - Mimics sepsis and other viral infections. High mortality rate

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

[1]Mularoni A et al, AJT 2025



© 2026 Infectious Disease Board Review

# HHV-8 Diagnosis and Treatment

- Diagnosis
  - HHV-8 IgG
  - HHV-8 PCR on plasma, tissue
  - Biopsy/pathology for primary effusion lymphoma, Castleman's disease, etc
    - HHV-8 immunohistochemistry
- Treatment
  - Reduction of immunosuppression (watch for rejection)/start antiretroviral therapy
  - mTor inhibitors (sirolimus/rapamycin, etc) for transplant patients
  - Antiviral therapies +/- efficacy, not usually recommended, can be considered
  - Intralesional therapy or adjuvant chemotherapy may be required if unresponsive to these conservative measures or for more aggressive disease
  - Kaposi's sarcoma treated as a cancer
  - KSHV Inflammatory Cytokine Syndrome (KICS) = foscarnet + rituximab
    - Rituximab: wider blockade of the cytokine cascade through the potential eradication of HHV-8-infected CD20. B cells; reducing the reservoir → limiting viral proliferation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Antiviral Prophylaxis & Treatment Agents

*acyclovir/valacyclovir/famciclovir and letermovir *for prophylaxis only*

**foscarnet, cidofovir, maribavir not usually used for prophylaxis

| Antiviral agent | CMV | EBV | HHV-6 | HHV-8 | HSV | Varicella | BK | Adeno-virus |
|---|---|---|---|---|---|---|---|---|
| **Commercially available** | | | | | | | | |
| acyclovir/valacyclovir/famciclovir* | high dose +/- | | | | x | x | | |
| ganciclovir IV/valganciclovir PO | x | | x | +/- | x | x | | |
| foscarnet** | x | | x | +/- | x | x | | |
| cidofovir** | x | | x | +/- | x | x | poor | +/- IC50 |
| letermovir (prophylaxis only) | **x** | | | | | | | |
| maribavir (treatment only) | **x** | *in vitro* | | | | | | |
| **Novel/investigational antiviral agents (SOT)** | | | | | | | | |
| *brincidofovir (not available)* | *x* | *x* | | | *x* | *x* | *x* | *x* |
| *pritelivir (phase III)* | | | | | *x* | | | |

Modified from Kotton CN, Updates on antiviral drugs for cytomegalovirus prevention and treatment, Curr Opin Organ Transplant 2019, 24:469–475

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**39**

# HIV-Associated Opportunistic Infections II

**Rajesh Gandhi, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# HIV-Associated Opportunistic Infections: Part II

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

Acknowledgement: Dr. Henry Masur for sharing slides

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## HIV Associated Opportunistic Infections: Part 2

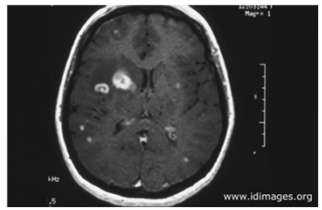
- **Opportunistic CNS Infections: Brain Lesions**
- **Cryptococcal Infections**
- **Mycobacterial Infections**
- **Immune Reconstitution Inflammatory Syndrome**
- **Cytomegalovirus (CMV)**

## Question #1

- 50-year-old M with HIV (CD4 40, HIV RNA 60,000 not on antiretroviral therapy) now with fever, headache
- Northeast US, no travel; no animal, TB exposures
- MRI: ring enhancing lesions; no midline shift
- Serum toxoplasma (toxo) IgG +

**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
E. Liposomal amphotericin and 5FC





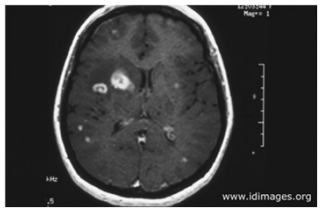

© 2026 Infectious Disease Board Review

## Question #1

- 50-year-old M with HIV (CD4 40, HIV RNA 60,000 not on antiretroviral therapy) now with fever, headache
- Northeast US, no travel; no animal, TB exposures
- MRI: ring enhancing lesions; no midline shift
- Serum toxoplasma (toxo) IgG +

### 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
E. Liposomal amphotericin and 5FC



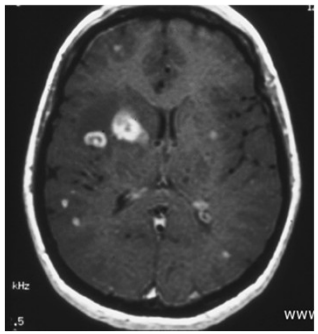

## Brain Lesions in People with HIV (PWH)




- MRI with contrast favored over CT (CT without contrast: 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

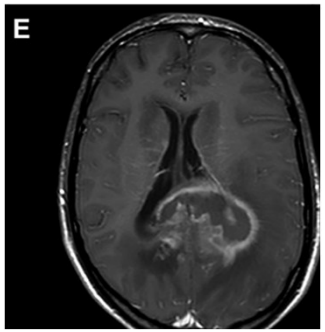
Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

### Toxoplasma Encephalitis



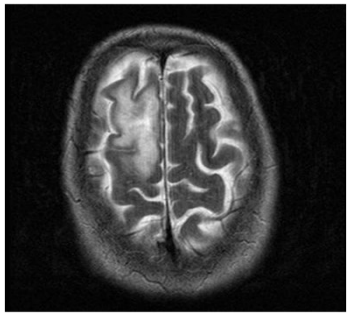

www.idimages.org

### Primary CNS Lymphoma

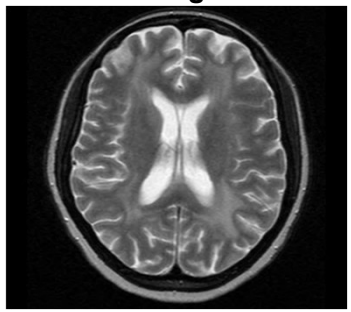



Siripurapu R and Ota Y, Neuroimag Clin N Am, 2023

### PML: Asymmetric White Matter Changes Adjacent to Cortical Ribbon No Mass



### HIV Encephalitis: Bilateral Symmetric White Matter Changes



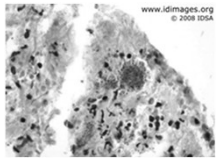
www.idimages.org. Contributed by Dr. Vince Marconi



© 2026 Infectious Disease Board Review

## Toxoplasma Encephalitis (TE)

- Caused by **protozoan, *Toxoplasma gondii***
- Reactivation of latent tissue cysts
- Highest risk is in PWH with **CD4 count <100**
- Headache, confusion, weakness, fever
- Diagnosis:
  - **Serum toxoplasma IgG usually positive**
  - **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

## Toxoplasma Encephalitis: Therapy

- **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

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

## Primary Prevention of Toxoplasmosis in 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

## Primary Prevention of Toxoplasmosis in PWH

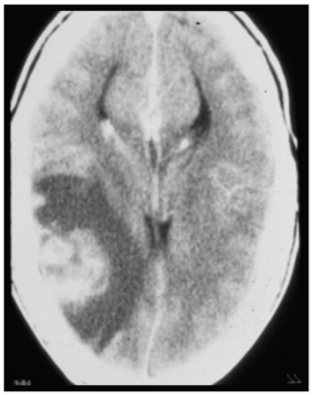
- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Nothing more is needed
- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine (plus leucovorin)
  - If on Aerosol pentamidine because cannot take TMP-SMX: not protected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

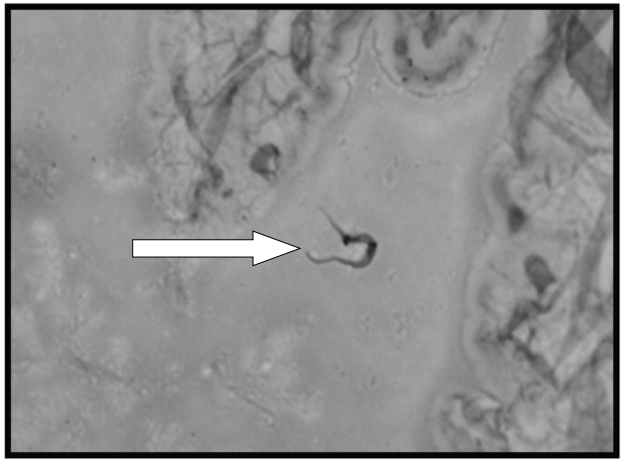
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/toxoplasma-gondii?view=full


© 2026 Infectious Disease Board Review

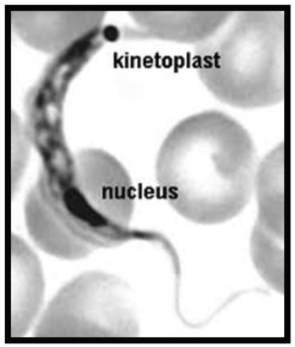
## Case Study

- A 39-year-old female from Brazil presents to ED with seizure.
  - HIV Ag/Ab positive
  - CD4 count 20/μL
  - HIV RNA 100,000 copies/μL
- Started on sulfadiazine, pyrimethamine.
- After 14 days, not improved; brain biopsy performed

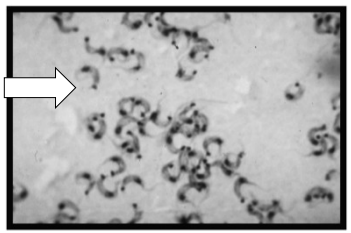




## Trypanosoma cruzi in Blood Smear and CSF (Chagasic Encephalitis in PWH)




**Flagellum**



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

**Cryptococcal Infections**


© 2026 Infectious Disease Board Review

## Question #2

- 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 same time as anti-fungal therapy
B. About 4 weeks after starting anti-fungal therapy
C. 10 weeks after starting anti-fungal therapy
D. 6 months after starting anti-fungal therapy
E. After completing maintenance anti-fungal therapy

## Question #2

- 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 same time as anti-fungal therapy
**B. About 4 weeks after starting anti-fungal therapy***
C. 10 weeks after starting anti-fungal therapy
D. 6 months after starting anti-fungal therapy
E. After completing maintenance anti-fungal therapy

## HIV-Associated Cryptococcal Meningitis

- Usually presents with **subacute onset** of confusion, lethargy
- Neck stiffness and photophobia only occur in 25%
- **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.
  - High sensitivity and specificity.
  - False positives uncommon (cross-reactive infection: Trichosporon species)
- Blood cultures positive for cryptococcus in 60%

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

## Therapy of Cryptococcal Meningitis

| | | | |
|---|---|---|---|
| **Liposomal Ampho B** **3-4 mg/kg daily** plus **Flucytosine*** **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**

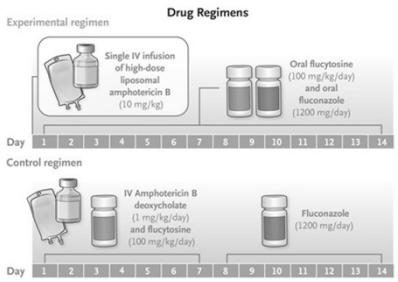
*****Stop after at least 1 yr total therapy if patient asymptomatic, CD4 >100, suppressed HIV RNA on ART**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

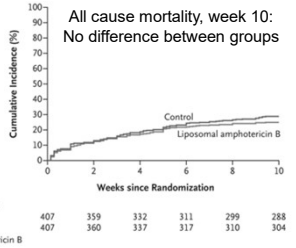

© 2026 Infectious Disease Board Review

## Single-dose Liposomal AmB with Fluconazole/5FC
Preferred in Resource-limited Health Care Systems (WHO)

AMBITION Trial (n=814 participants)




All cause mortality, week 10:
No difference between groups




**Adverse events less frequent in single-dose AmB group**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jarvis JN et al, NEJM, 2022

## Management of Cryptococcal Meningitis

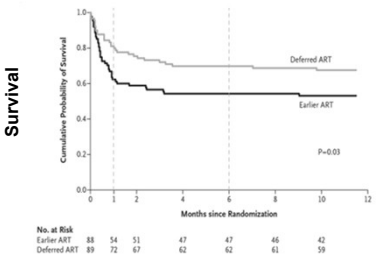
- Patients in hospital for at least 7 days and ideally 14 days
- Lumbar puncture at day 7 and 14
- In patients with symptoms of elevated intracranial pressure and opening pressure >25 cm: remove CSF to reduce pressure by half or <20cm H20
  - Lumbar drain or VP shunt may be needed if pressures remain elevated
- Successful induction therapy = clinical improvement, negative CSF culture
- 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

## When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines: 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi RT et al, IAS USA Guidelines, JAMA 2024

## Preventing Disease
***(Pre-emptive Therapy for Cryptococcal Ag+/ Low CD4 Cell Count)***

- **Patients with CD4 count <200: check serum cryptococcal antigen**
  - Frequency of + Ag: 2.9% if CD4 <100
  - 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 ≥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


© 2026 Infectious Disease Board Review

## EFFECT Trial: Fluconazole ± Flucytosine for HIV-Associated Cryptococcal Antigenemia

**Phase 3, open-label**
**PWH and CD4 <100**
**Blood CrAg+**
**CSF CrAg- (or LP declined)**

Randomization 1:1

**Fluconazole + Flucytosine (n=304)**

**Fluconazole Alone (n=300)**

**Fluconazole Alone**

Day 0 — Day 14

**Key Results**

- 6-month mortality
  - Fluconazole + Flucytosine: 13%
  - Fluconazole alone: 17%
- Trend towards increased efficacy in combination arm in participants with high CrAg titer (although numbers small)
- Fluconazole monotherapy still standard; more research needed

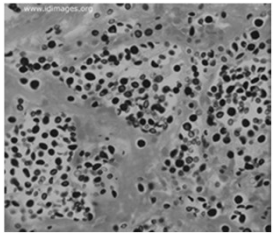
Murphy KL, et al. AIDS 2026. Abstract OAC4206LB.

## Cryptococcal Prostate Abscess

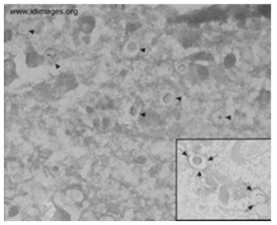
- Man with advanced HIV, CD4 cell count 40, HIV RNA 225,000 (not on ART) presented with 4 weeks of pain on defecation



Pelvic CT Scan: Prostate Abscess



Silver Stain of Prostatic Aspirate



Hematoxylin and Eosin Stain

www.idimages.org

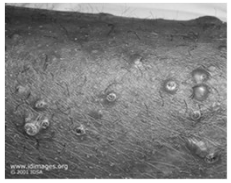
## Mucocutaneous Cryptococcus

Man with advanced HIV, CD4 count <20 (not on ART) presented with fever, cough and skin lesions





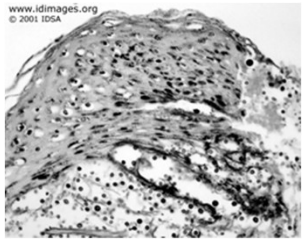




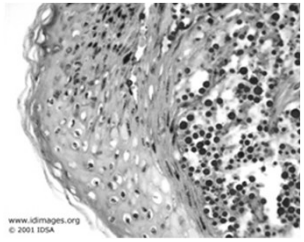

www.idimages.org

## 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



© 2026 Infectious Disease Board Review

## Mycobacterial Infections

## Tuberculosis in PWH: Highlights

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

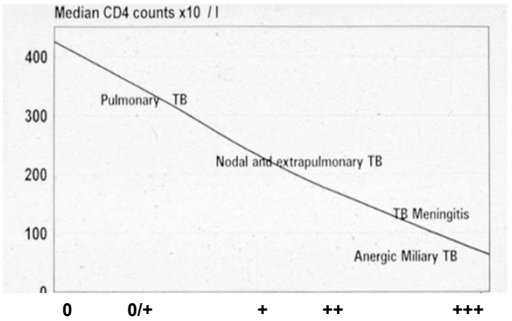
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium?view=full
Torok et al, CID, 2011; Meintjes NEJM, 2018

## Antiretroviral /TB Drug Interactions: Selected

| TB Drug | Antiretrovirals |
|---|---|
| Isoniazid | •No interactions |
| Rifampin | •Nucleoside RT inhibitors (TAF with caution)<br>•Dolutegravir, Raltegravir: twice daily<br>•Protease inhibitors: not recommended |
| Rifabutin | •Nucleoside RT inhibitors (TAF with caution)<br>•Dolutegravir, Raltegravir – no change in dose<br>•PIs with RTV – dose adjust rifabutin<br>•PIs with cobicistat – do not coadminister |
| Pyrazinamide, Ethambutol, Moxifloxacin | •No interactions |

Adapted by Dr Barbara Taylor from: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection.

## 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


© 2026 Infectious Disease Board Review

## Question #3

- 45-yo man with HIV (CD4 11, HIV RNA 300,000); fever, diarrhea and weight loss.
- No known TB exposure
- Started on dolutegravir + tenofovir/emtricitabine
- 2 wk later: enlarged supraclavicular lymph node
- Biopsy: necrotizing granulomas and AFB

**What would you recommend?**

A. Stop ART; initiate treatment for MAC
B. Stop ART; initiate MAC treatment, steroids
C. Continue ART; initiate treatment for MAC
D. Continue ART; start MAC treatment plus steroids
E. Start steroids; stop all other treatments



Image from Riddell J, J Translational Med, 2007

## Question #3

- 45-yo man with HIV (CD4 11, HIV RNA 300,000); fever, diarrhea and weight loss.
- No known TB exposure
- Started on dolutegravir + tenofovir/emtricitabine
- 2 wk later: enlarged supraclavicular lymph node
- Biopsy: necrotizing granulomas and AFB

**What would you recommend?**

A. Stop ART; initiate treatment for MAC
B. Stop ART; initiate MAC treatment, steroids
**C. Continue ART; initiate treatment for MAC***
D. Continue ART; start MAC treatment plus steroids
E. Start steroids; stop all other treatments



Image from Riddell J, J Translational Med, 2007

## Mycobacterium Avium Complex

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

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

## Diagnosis

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

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


© 2026 Infectious Disease Board Review

## Treatment for MAC

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

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

## ~~Primary MAC Prophylaxis~~

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

**Immune Reconstitution Inflammatory Syndrome (IRIS)**



## Immune Reconstitution Inflammatory Syndrome (IRIS)

- 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


© 2026 Infectious Disease Board Review

## 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**
  - Fevers and worsening of underlying OI or tumor
  - Usually 4-8 weeks after ART initiation; may be earlier (few days) or later

## Mycobacterial IRIS

| Pathogen | Typical/Characteristics of the Disease |
|---|---|
| **Mycobacterium tuberculosis** | • Worsening lung infiltrates, lymphadenitis, CNS tuberculomas |
| **MAC** | • Lymphadenitis; pulmonary and abdominal disease.<br>• Bacteremia generally absent.<br>• Elevated alkaline phosphatase may be predictive.<br>• Severe forms of MAC IRIS with hemophagocytic lymphohistiocytosis phenotype may occur |

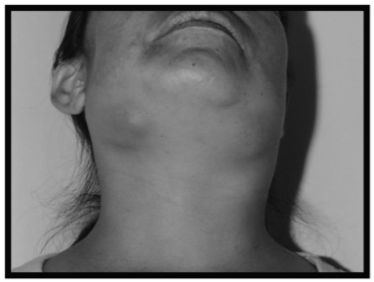
Cecil Medicine Textbook (French and Meintjes)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/disseminated?view=full

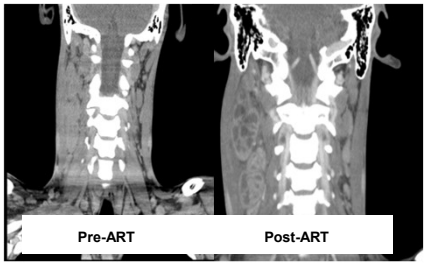
## Examples of IRIS

| 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

## MAC IRIS in a Person with HIV






Sereti I, IAS USA Topics in Antiviral Medicine, 2019


© 2026 Infectious Disease Board Review

## Management of IRIS

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

**Cytomegalovirus (CMV)**

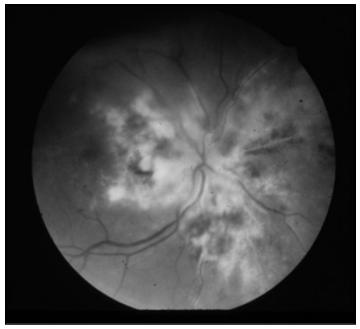
## CMV in PWH: Highlights

- PWH who have CD4 count <50 and are not receiving ART
- End-organ disease:
  - Retinitis
  - GI: Colitis, Esophagitis
  - Neurologic disease
  - Pneumonitis: rare; when CMV found in bronchoalveolar lavage, frequently bystander
- Prevention: ART; valganciclovir prophylaxis NOT recommended

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

## CMV Retinitis

- **Visual changes, decreased visual acuity**
- **Fundoscopic 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

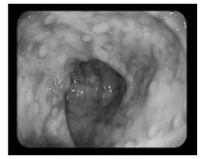

© 2026 Infectious Disease Board Review

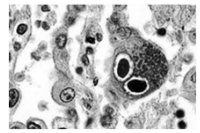
## Therapy for CMV Retinitis

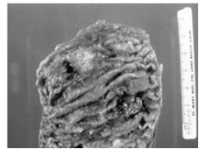
- **Immediate sight-threatening lesions**
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (twice daily x 14–21 days), then daily for at least 3-6 months plus
  - Intravitreal ganciclovir weekly over several weeks until lesion inactivity
  - Ganciclovir implant no longer manufactured
- **Small 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

## 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/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

## 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

## Summary

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

**New approaches to treating and preventing cryptococcal meningitis; deferring ART for about 4 weeks appropriate**

**High risk of TB reactivation; MAC Prophylaxis no longer recommended when ART started quickly**

**Immune Reconstitution Inflammatory Syndrome: paradoxical worsening or unmasking of subclinical disease**

**CMV end-organ disease when CD4 count <50: retinitis, GI infection (colitis), neurologic disease**


© 2026 Infectious Disease Board Review

## For More Content:

**HIV Associated Opportunistic Infections: Part 3 (Online)**

- **Mucocutaneous Infections: Candida, VZV, HSV, EBV**
- **Endemic Mycoses**
- **Gastrointestinal (GI) Complications**


© 2026 Infectious Disease Board Review

# Therapy of Cryptococcal Meningitis

| | | | |
|---|---|---|---|
| **Liposomal Ampho B** | **3-4 mg/kg daily** | | |
| plus | | | |
| **Flucytosine*** | **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**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

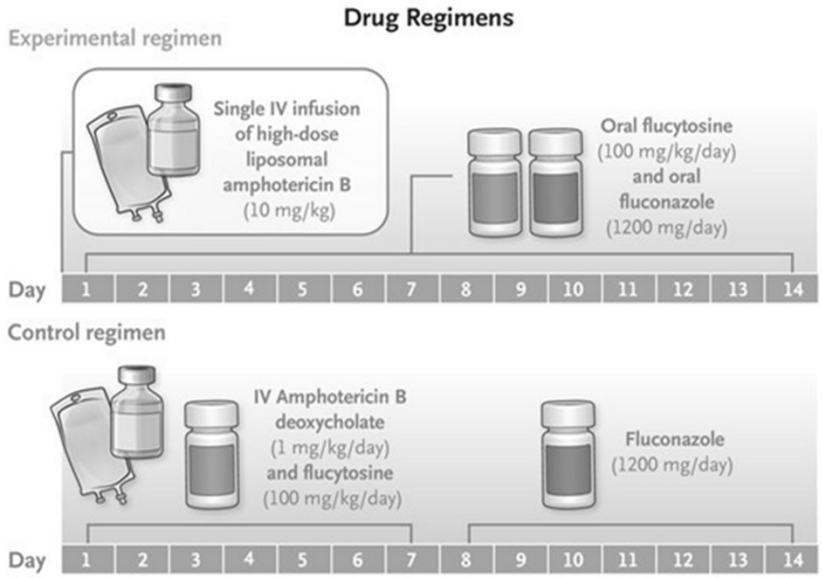


© 2026 Infectious Disease Board Review

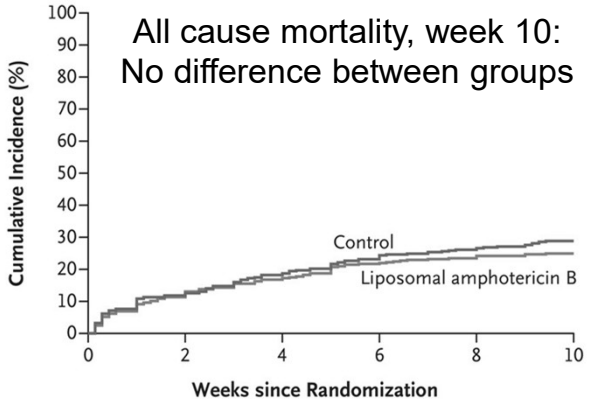
# Single-dose Liposomal AmB with Fluconazole/5FC

Preferred in Resource-limited Health Care Systems (WHO)

AMBITION Trial (n=814 participants)




All cause mortality, week 10:
No difference between groups




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Control | 407 | 359 | 332 | 311 | 299 | 288 |
| Liposomal amphotericin B | 407 | 360 | 337 | 317 | 310 | 304 |

**Adverse events less frequent in single-dose AmB group**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jarvis JN et al, NEJM, 2022

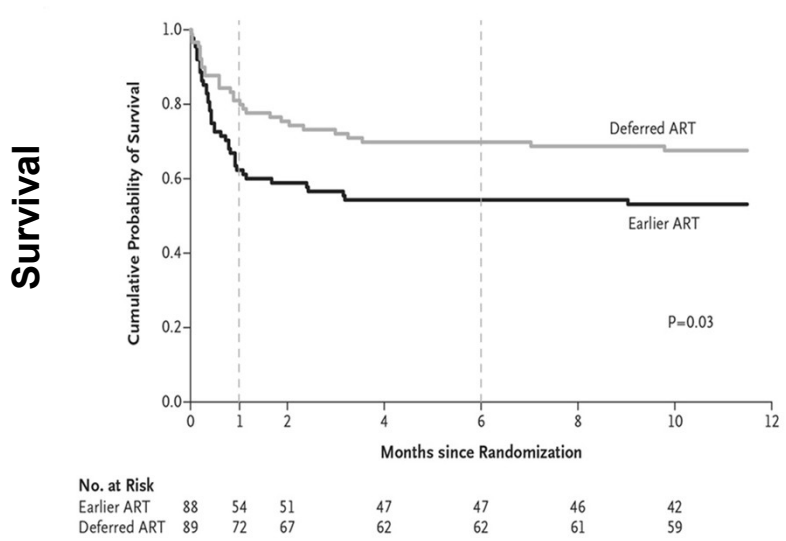


© 2026 Infectious Disease Board Review

# When to Start ART for Cryptococcal Meningitis

- DHHS OI Guidelines: 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gandhi RT et al, IAS USA Guidelines, JAMA 2024



© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**40**

# Syndromes Masquerading as Infections

**Karen Bloch, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Syndromes that Masquerade as Infections

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

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None



With Appreciation to
Dr. Bennett Lorber

## ID Board Content Distribution

| CONTENT CATEGORY | BLUEPRINT % |
|---|---|
| Bacterial Disease | 27% |
| Human Immunodeficiency Virus (HIV) | 15% |
| Antimicrobial Therapy | 9% |
| Viral Diseases | 7% |
| Travel and Tropical Medicine | 5% |
| Fungi | 5% |
| Immunocompromised Host (Non-HIV Infection) | 5% |
| Vaccinations | 4% |
| Infection Prevention and Control | 5% |
| Internal Medicine and Non-Infectious Syndromes | 18% |
| Total | 100% |

MARCH 2026

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## General Internal Medicine-1

| INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES *(18% of exam)* | | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** | | | | | |
| Malignancies | | HIGH | MEDIUM | MEDIUM | LOW |
| Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome) | LF | MEDIUM | MEDIUM | MEDIUM | LOW |
| Noninfectious inflammatory disorders (e.g., vasculitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, aortitis) | | HIGH | MEDIUM | MEDIUM | MEDIUM |
| Dermatologic disorders | | HIGH | MEDIUM | MEDIUM | LOW |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## General Internal Medicine-2

| INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES *continued...* *(18% of exam)* | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** *continued...* | | | | |
| Hematologic disorders | MEDIUM | MEDIUM | MEDIUM | MEDIUM |
| Noninfectious central nervous system disease | MEDIUM | MEDIUM | MEDIUM | LOW |
| Bites, stings, and toxins | MEDIUM | MEDIUM | MEDIUM | LOW |
| Drug fever | HIGH | HIGH | MEDIUM | LOW |
| Ethical and legal decision making | *Not Applicable* | MEDIUM | MEDIUM | *Not Applicable* |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## IM and Non-Infectious Syndromes

- Surgical Infections
- Critical Care Medicine
  - SIRS
  - VAP
  - ARDS/eosinophilic pneumonia
  - Hyperthermia/hypothermia

## Mimics

- Many conditions masquerade as infections
  - Fever almost universally present
  - Sometimes focal abnormality
    - Cellulitis vs. stasis dermatitis
    - Viral vs. Organizing Pneumonia
    - Lymphadenitis vs. Lymphoma
  - ID likely to be consulted!

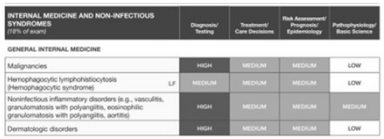


**vs.**



## Test Taking Tips

- Emphasis on high-importance content (70% of Q)
- For non-infectious syndromes, this is heavily skewed toward diagnosis
  - Limited emphasis on treatment, epidemiology or prognosis
  - No questions on pathophysiology



| INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES *(18% of exam)* | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** | | | | |
| Malignancies | HIGH | MEDIUM | MEDIUM | LOW |
| Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome) LF | MEDIUM | MEDIUM | MEDIUM | LOW |
| Noninfectious inflammatory disorders (e.g., vasculitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, aortitis) | HIGH | MEDIUM | MEDIUM | MEDIUM |
| Dermatologic disorders | HIGH | MEDIUM | MEDIUM | LOW |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**40 Syndromes that Masquerade as Infections**

*Speaker: Karen Bloch, MD*

© 2026 Infectious Disease Board Review

## Test Taking Tip

- Just as for infections, look for “buzzwords” and “hooks” in red font in the lecture
- For infections:
  - If I say, “skinned rabbit”, you say…

## Test Taking Tip

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



(Pulmonary) TULAREMIA

## Test Taking Tip

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

You say…..



## Test Taking Tip

If I say, “chitterlings”

You say…..



**YERSINIA (gastroenteritis)**


© 2026 Infectious Disease Board Review

## Test Taking Tip

If I say, ”Bull’s-eye rash”

You say…..



## Test Taking Tip

If I say, ”Bull’s-eye rash”

You say…..



**Lyme disease**
(or **Erythema migrans** or **STARI**)

## My Approach to Mimics

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

## Cases




© 2026 Infectious Disease Board Review

## Question #1

- 26-year-old man presents with a 1-month h/o fever, night sweats and 10 lb. weight loss
- This started with a sore throat, but RADT was negative for Strep, and pharyngitis has resolved
- He lives in Indiana with his wife and 2 yo son, who are healthy. They have 2 cats.

## Question #1

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

## Question #1

### What is the most likely cause of this presentation?

A. Lymphoma
B. Rheumatic fever
C. Acute EBV infection
D. Bartonella endocarditis
E. Histoplasmosis

## Question #1

### What is the most likely cause of this presentation?

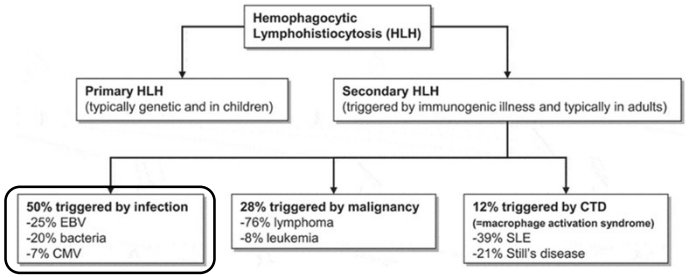
A. Lymphoma
B. Rheumatic fever
**C. Acute EBV infection***
D. Bartonella endocarditis
E. Histoplasmosis


© 2026 Infectious Disease Board Review

## Hemophagocytic Lymphohistiocytosis

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

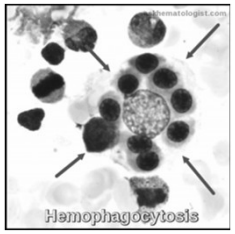
## HLH & Infection




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## HLH-2024: Diagnostic Criteria

- At least **5/7** of the following:
  - Fever (T>38.5°C)
  - Splenomegaly
  - Cytopenias (2/3 lineages)
  - Hypertriglyceridemia (>3mmol/L) and/or hypofibrinogenemia
  - Ferritin >500 mcg/mL
  - Elevated soluble IL-2 receptor (aka sCD25)
  - NK cell function now a functional criteria




## HLH Pearls

- Antecedent mono that doesn't get better
- Cytopenias
- Elevated ferritin
- Treating an underlying infection is often curative


© 2026 Infectious Disease Board Review

## Question #2

- 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

## Question #2

### 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 her underwear waistband



## Question #2

- 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 negative
- On afternoon rounds with the attending, the fever has resolved with Tylenol, and the rash is no longer present

## Question #2

### Which of the following would support the diagnosis?

A. Elevated eosinophils
B. Koebner phenomenon
C. Positive hepatitis B antigen
D. Elevated LDH
E. Elevated ASO titer


© 2026 Infectious Disease Board Review

## Question #2

### Which of the following would support the diagnosis?

A. Elevated eosinophils
**B. Koebner phenomenon***
C. Positive hepatitis B antigen
D. Elevated LDH
E. Elevated ASO titer

## Adult Still's Disease (Adult-Onset JRA)

Yamaguchi Criteria: (5 features with 2 major criteria)

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

## Adult Still's Disease

• Buzzwords and associations:

**Evanescent, salmon-colored** rash



=



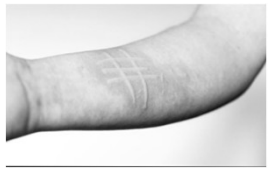
## Adult Still's Disease

• Buzzwords and associations:

**Koebner phenomenon**

Rash at pressure sites (bra/underwear)

Can be trivial such as hot shower







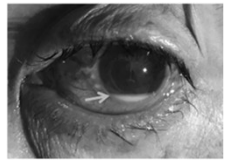
© 2026 Infectious Disease Board Review

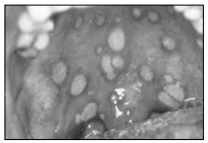
## Question #3

- 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.

## Question #3

- 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





## Question #3

### Which would support the diagnosis?

A. HSV PCR
B. Biopsy of oral ulcer
C. Papule at site of venipuncture
D. Painful inguinal lymph node
E. Histoplasma antigen

## Question #3

### Which would support the diagnosis?

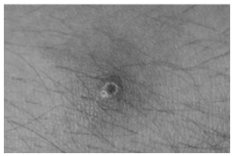
A. HSV PCR
B. Biopsy of oral ulcer
**C. Papule at site of venipuncture***
D. Painful inguinal lymph node
E. Histoplasma antigen


© 2026 Infectious Disease Board Review

## Behçet's Disease

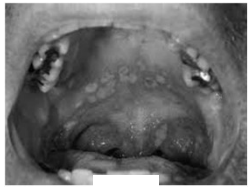


- Pleomorphic vasculitis diagnosed clinically
- Recurrent oral ulcers (>3 per year) PLUS 2 of the following
- Recurrent genital ulcers
- Eye (uveitis, retinitis, hypopyon)
- Skin lesions, esp pathergy



- Less common manifestations
  - GI disease (abdominal pain, bloody diarrhea)
  - Aseptic meningitis
  - Arterial and venous thrombosis

## 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



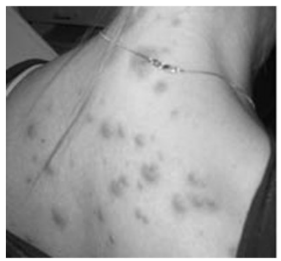
## Question #4

- 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

## Question #4

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




© 2026 Infectious Disease Board Review

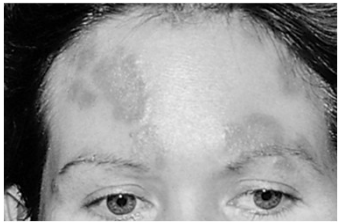
## Question #4

Hospital Day 3:

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

Hospital Day 4:

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



## Question #4

### Which is most likely to be diagnostic?

A. Flow cytometry
B. Naproxen challenge
C. Bone marrow biopsy
D. Skin biopsy
E. PET scan

## Question #4

### Which is most likely to be diagnostic?

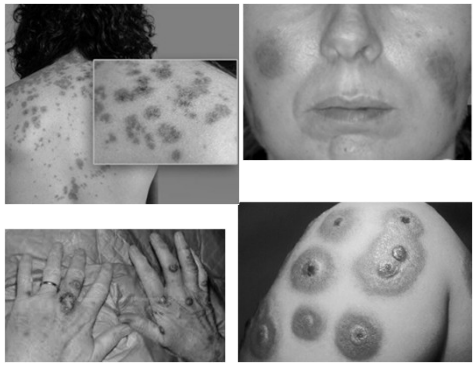
A. Flow cytometry
B. Naproxen challenge
C. Bone marrow biopsy
**D. Skin biopsy***
E. PET scan

## 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


© 2026 Infectious Disease Board Review

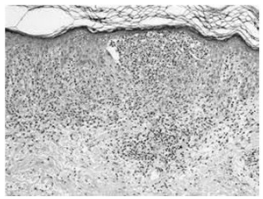
## Skin Lesions in Sweet Syndrome



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

## Sweet Syndrome

- 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

## Question #5

- 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

## Question #5

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




© 2026 Infectious Disease Board Review

## Question #5

### 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

## Question #5

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

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

## Pyoderma gangrenosum

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

## Pyoderma gangrenosum

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




© 2026 Infectious Disease Board Review

## Question #6

- A 79-year-old woman is seen for 3 weeks of headache, 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



## Question #6

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

## Question #6

### Which of the following is most likely to be diagnostic?

A. Temporal artery ultrasound
B. Taenia solium serology
C. TTE
D. CT angiography
E. Temporal artery biopsy

## Question #6

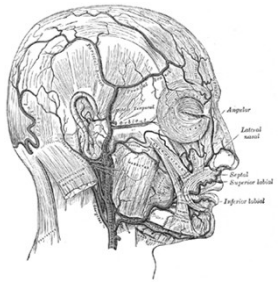
### Which of the following is most likely to be diagnostic?

A. Temporal artery ultrasound
B. Taenia solium serology
C. TTE
D. CT angiography
**E. Temporal artery biopsy***


© 2026 Infectious Disease Board Review

## Giant Cell Arteritis

- Extracranial branches of the carotid
- Criteria (ACR 1990): 3/5 sensi 93%
  - Age >50 years
  - New onset HA
  - Temporal artery tenderness/dec pulse
  - ESR >50 mm/h
  - Abnl temporal biopsy (vasculitis)
    - > 2 cm with multiple sections reviewed
    - Steroids <2 weeks do not reduce yield and may be sight-saving
- TA u/s, PET, or CT angiography alternative options if biopsy not diagnostic



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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

Empiric steroids indicated when suspicion is high

## Overlap of GCA and PMR

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



## Takayasu Arteritis



- Large vessel vasculitis
  - Aorta, carotids and pulmonary arteries
- 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: Angiography



© 2026 Infectious Disease Board Review

## Question #7

- 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.

## Question #7

- 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



## Question #7

**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

## Question #7

**Which of the following is most likely to be diagnostic?**

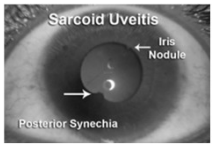
**A. Chest x-ray***
B. Serology for Borrelia burgdorferi
C. Urine Histoplasma antigen
D. Arthrocentesis
E. Skin biopsy


© 2026 Infectious Disease Board Review

## Sarcoidosis

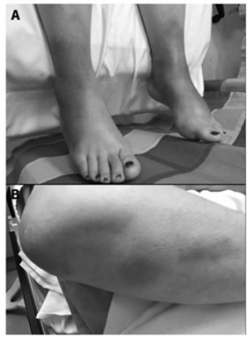
- Extra-pulmonary disease in ~1/3 of cases
- Lofgren Syndrome
  - Only form of sarcoid that is a clinical diagnosis
  - Triad of hilar LAN, acute arthritis, EN
  - Women, ankles (>90%), fevers common
- BUZZWORDS
  - Hilar LAN, EN, uveitis, parotid enlargement
  - Non-caseating granulomas
  - Aseptic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





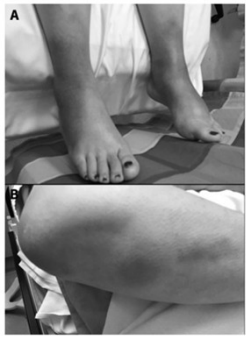

## Erythema nodosum

- NO cause >50% of cases
- Drugs: sulfonamides, penicillins
- Oral contraceptives
- Sarcoid (Lofgren's syndrome)
- Ulcerative colitis (or Crohn's or Bechets)
- Microbes:
  - Streptococci (16% EN cases), Bartonella, TB
  - Endemic fungi
  - EBV, Hep B/C, covid-19




## Erythema nodosum

- **NO** cause >50% of cases
- **D**rugs: sulfonamides, penicillins
- **O**ral contraceptives
- **S**arcoid (Lofgren's syndrome)
- **U**lcerative colitis (or Crohn's or Bechets)
- **M**icrobes:
  - Streptococci (16% EN cases), Bartonella, TB
  - Endemic fungi
  - EBV, Hep B/C, covid-19




## Question #8

- A 19-year-old Iraqi immigrant is admitted with 2-days 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


© 2026 Infectious Disease Board Review

## Question #8

### Which of the following is most likely to be diagnostic?

A. Family history
B. Colonoscopy
C. Genetic testing
D. Angiography
E. ANCA blood test

## Question #8

### Which of the following is most likely to be diagnostic?

A. Family history
B. Colonoscopy
**C. Genetic testing***
D. Angiography
E. ANCA blood test

## Familial Mediterranean Fever

- Auto-inflammatory disease causing a periodic fever syndrome
  - Others: PFAPA, TRAPS, hyperimmunoglobulin D
- Recurrent attacks (1-3 days) of fever & serositis (peritonitis, pleuritis, pericarditis, arthritis)
- Mediterranean ancestry
- Dx:
  - Biallelic mutation of MEFV gene
  - Suggestive: response to colchicine
  - FH insensitive (AR disease)




## FMF Buzz Words

- Mediterranean ancestry
  - Southern Europe (Greece, Italy, Spain, Balkans)
  - Turkey, Middle East
  - North Africa
- Periodic, self-limited fevers
- Serositis




© 2026 Infectious Disease Board Review

## Question #9

- 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.



## Question #9

- 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

## Question #9

- Serologic studies:
  - EBV IgM negative
  - HIV negative
  - CMV, Toxo, Bartonella negative
  - RF, ANA, ds-DNA negative
- Lymph node biopsy is performed; Stains for AFB and fungi negative

## Question #9

**Which of the following is a lymph node biopsy is most likely to show?**

A. Stellate necrosis
B. Multinucleated giant cells
C. Non-necrotizing granulomas
D. Necrotizing histiocytosis
E. Reed-Sternberg cells


© 2026 Infectious Disease Board Review

## Question #9

**Which of the following is a lymph node biopsy is most likely to show?**

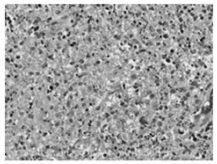
A. Stellate necrosis
B. Multinucleated giant cells
C. Non-necrotizing granulomas
**D. Necrotizing histiocytosis***
E. Reed-Sternberg cells

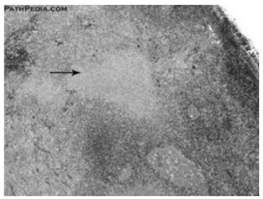
## Kikuchi Disease

- AKA acute necrotizing histiocytic lymphadenitis
- Self-limited condition of unknown cause
- Typically occurs in young women
- May follow infection (EBV, COVID-19)
- Fever & cervical LAN (esp posterior, usually unilateral)
- Rarely: morbilliform rash, diffuse LAN, aseptic meningitis, uveitis
- Leukopenia & atypical lymphocytes in 25% of cases

## Kikuchi Disease

- Diagnosis by pathology:
  - Necrotizing histiocytic infiltrate (not neutrophils) and fragments of nuclear debris
- Buzzwords and associations:
  - Cervical adenopathy in young woman
  - Atypical lymphocytes (mono-like syndrome)
  - Path: necrotizing adenitis with histiocytosis





## Question #10

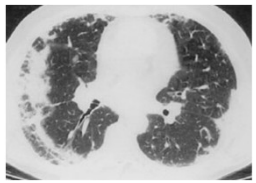
- A 41-year-old woman is seen for fever, worsening respiratory symptoms, and a rash.
- She has long-standing asthma with frequent exacerbations.
- She uses an inhaler several times a day and was recently placed on a leukotriene receptor antagonist. She is being tapered off steroids which she has taken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


© 2026 Infectious Disease Board Review

## Question #10

- 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





## Question #10

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

A. Strongyloidiasis
B. Allergic reaction to Montelukast
C. Sarcoidosis
D. Allergic bronchopulmonary aspergillosis
E. Eosinophilic granulomatosis with polyangiitis

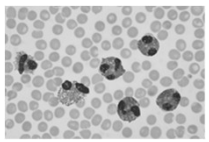
## Question #10

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

A. Strongyloidiasis
B. Allergic reaction to Montelukast
C. Sarcoidosis
D. Allergic bronchopulmonary aspergillosis
**E. Eosinophilic granulomatosis with polyangiitis***

## EGPA (Churg-Strauss)

- Eosinophilic granulomatosis with polyangiitis
- Small vessel vasculitis associated with allergic rhinitis, asthma, peripheral and lung eosinophilia
- Most often involves lung and skin, but can involve heart, GI tract, and nervous system
- Labs may be helpful here
  - Eos usually >10%
  - IgE often elevated
  - P-ANCA positive in only 30-40% of EGPA patients
- Tapering of steroids often “unmasks” EGPA



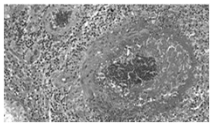

© 2026 Infectious Disease Board Review

## EGPA

2022 ACR/EULAR Classification: >6 points c/w diagnosis

| Criterion | Points |
|---|---|
| Eosinophilia (≥1 x10⁹/L) | 5 |
| Obstructive lung disease | 3 |
| Nasal polyps | 3 |
| Extravascular eosinophilic inflammation | 2 |
| Mononeuritis multiplex/motor neuropathy | 1 |
| Negative points:<br>• Pos c-ANCA or anti-proteinase 3<br>• Hematuria | <br>Minus 3<br>Minus 1 |





## EGPA

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

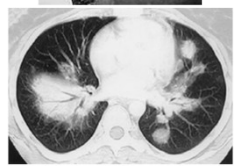
## Question #11

- 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 admits to use of intranasal cocaine in last 2 months

## Question #11

- 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






© 2026 Infectious Disease Board Review

## Question #11

**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

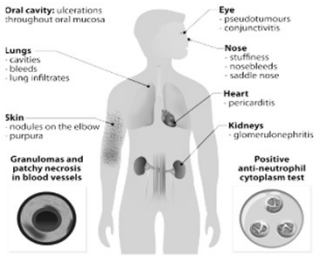
## Question #11

**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

## 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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 2022 ACR/EULAR Criteria for GPA

| Criterion | Points |
|---|---|
| Pos c-ANCA or anti-proteinase 3 | 5 |
| Nasal findings<br>• symptoms (drainage, congestion)<br>• Imaging (consolidations, inflammation) | <br>3<br>1 |
| Cartilaginous abnl (nasal or auricular) | 2 |
| Pulmonary nodules or cavities | 2 |
| Granulomas or giant cells on bx | 2 |
| Pauci-immune glomerulonephritis | 1 |
| Negative points:<br>•Eosinophilia<br>•P-ANCA or anti-myeloperoxidase positivity | <br>Minus 4<br>Minus 1 |

≥5 diagnostic

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

## GPA vs EGPA: Pearls

| Feature | GPA | EGPA |
|---|---|---|
| Pulmonary | Nodules, cavitation, infiltrate | h/o Asthma, infiltrates |
| Sinuses | Chronic sinusitis/destruction | Chronic sinusitis, polyps |
| Kidneys | Pauci-immune GN | Rare |
| CNS | Rare | Neuropathy |
| Eos | No | Yes (peripheral and tissue) |
| ANCA | C-ANCA/PR3 positive (85%) | P-ANCA (<40%) |

## Question #12

- 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.

## Question #12

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





## Question #12

**Which of the following is most likely to be diagnostic?**

A. ANA
B. Comprehensive H&P
C. ACE level
D. CRP
E. Rheumatoid factor


© 2026 Infectious Disease Board Review

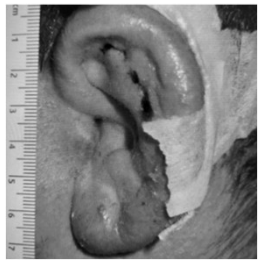
## Question #12

### Which of the following is most likely to be diagnostic?

A. ANA
**B. Comprehensive H&P***
C. ACE level
D. CRP
E. Rheumatoid factor

## Relapsing Polychondritis (RPC)

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



## RPC Diagnostic Criteria

**Criteria**

- Bilat auricular chondritis
- Seronegative polyarthritis
- Nasal chondritis
- Ocular inflammation
- Upper resp chondritis
- Cochlear and/or vestibular dysfunction

**Scores**

- 3 clinical criteria

OR

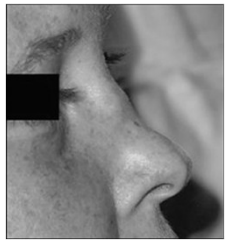
- 1 clinical criteria plus histopath

OR

- Chondritis at 2 or more locations responding to steroids and/or dapsone

## Saddle-nose Deformity

- Collapse of nasal bridge
  - GPA
  - Relapsing polychondritis
  - Lepromatous leprosy
  - Congenital syphilis
  - Cocaine use
  - Trauma




© 2026 Infectious Disease Board Review

## Relapsing Polychondritis

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



## Question #13

- A 29-year-old woman presents following a T-C seizure
- Her family notes that she has been c/o headache and increasingly paranoid in the last 2 weeks
- On exam, she is afebrile but confused. Note is made of involuntary twitching of both upper extremities
- Non-contrast head CT is unrevealing
- LP shows a CSF WBC of 22 (50% lymphocytes)

## Question #13

**Which of the following is most likely to impact management?**

A. Contrasted MRI of the brain
B. CSF ACE level
C. Anti-thyroid antibodies
D. Meningo-encephalitis PCR panel
E. CT of the abdo-pelvis

## Question #13

**Which of the following is most likely to impact management?**

A. Contrasted MRI of the brain
B. CSF ACE level
C. Anti-thyroid antibodies
D. Meningo-encephalitis PCR panel
**E. CT of the abdo-pelvis***


© 2026 Infectious Disease Board Review

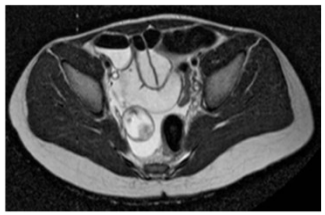
## Anti-NMDAR Encephalitis

- Autoimmune encephalitis
- Epidemiology:
  - Median age 21 years (children/young adults predominate)
  - Women>>Men (80% of premenopausal adults are female)
- Triggers
  - Ovarian teratomas (present in~50% of women age 12-44 years)
  - HSV-1 encephalitis (para-infectious)



## Anti-NMDAR Encephalitis

- Clinical presentation
  - Psychiatric symptoms in ~90% of teens/adults
  - Mutism or aphasia, pressured speech
  - Movement disorders
  - Autonomic instability
  - Seizures
- Treatment
  - Immunomodulators
  - PLEX
  - **Teratoma removal!**



## Karen.bloch@vumc.org





© 2026 Infectious Disease Board Review

# ID Board Content Distribution

| CONTENT CATEGORY | BLUEPRINT % |
|---|---|
| Bacterial Disease | 27% |
| Human Immunodeficiency Virus (HIV) | 15% |
| Antimicrobial Therapy | 9% |
| Viral Diseases | 7% |
| Travel and Tropical Medicine | 5% |
| Fungi | 5% |
| Immunocompromised Host (Non-HIV Infection) | 5% |
| Vaccinations | 4% |
| Infection Prevention and Control | 5% |
| Internal Medicine and Non-Infectious Syndromes | 18% |
| **Total** | **100%** |

MARCH 2026

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# General Internal Medicine-1

| INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES *(18% of exam)* | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** | | | | |
| Malignancies | HIGH | MEDIUM | MEDIUM | LOW |
| Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome) LF | MEDIUM | MEDIUM | MEDIUM | LOW |
| Noninfectious inflammatory disorders (e.g., vasculitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, aortitis) | HIGH | MEDIUM | MEDIUM | MEDIUM |
| Dermatologic disorders | HIGH | MEDIUM | MEDIUM | LOW |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# General Internal Medicine-2

| **INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES** *continued…* *(18% of exam)* | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** *continued…* | | | | |
| Hematologic disorders | MEDIUM | MEDIUM | MEDIUM | MEDIUM |
| Noninfectious central nervous system disease | MEDIUM | MEDIUM | MEDIUM | LOW |
| Bites, stings, and toxins | MEDIUM | MEDIUM | MEDIUM | LOW |
| Drug fever | HIGH | HIGH | MEDIUM | LOW |
| Ethical and legal decision making | *Not Applicable* | MEDIUM | MEDIUM | *Not Applicable* |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Test Taking Tips

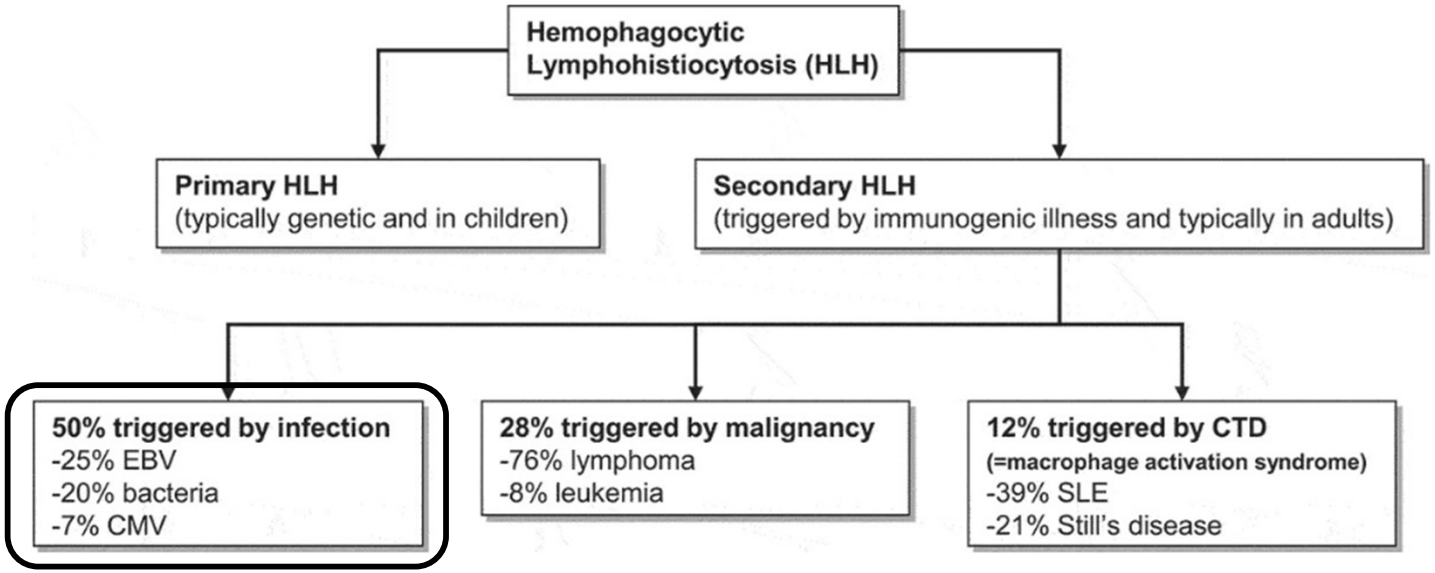
- Emphasis on high-importance content (70% of Q)
- For non-infectious syndromes, this is heavily skewed toward diagnosis
  - Limited emphasis on treatment, epidemiology or prognosis
  - No questions on pathophysiology

| INTERNAL MEDICINE AND NON-INFECTIOUS SYNDROMES *(18% of exam)* | Diagnosis/ Testing | Treatment/ Care Decisions | Risk Assessment/ Prognosis/ Epidemiology | Pathophysiology/ Basic Science |
|---|---|---|---|---|
| **GENERAL INTERNAL MEDICINE** | | | | |
| Malignancies | HIGH | MEDIUM | MEDIUM | LOW |
| Hemophagocytic lymphohistiocytosis (Hemophagocytic syndrome) LF | MEDIUM | MEDIUM | MEDIUM | LOW |
| Noninfectious inflammatory disorders (e.g., vasculitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, aortitis) | HIGH | MEDIUM | MEDIUM | MEDIUM |
| Dermatologic disorders | HIGH | MEDIUM | MEDIUM | LOW |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# HLH & Infection

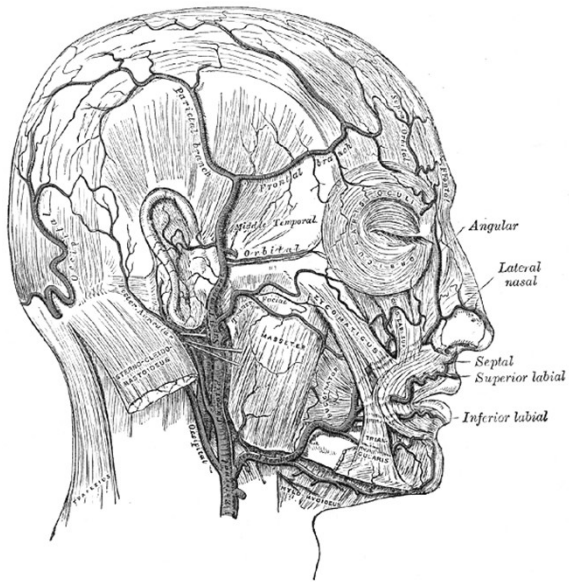



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Giant Cell Arteritis

- Extracranial branches of the carotid
- Criteria (ACR 1990): 3/5 sensi 93%
  - Age >50 years
  - New onset HA
  - Temporal artery tenderness/dec pulse
  - ESR >50 mm/h
  - Abnl temporal biopsy (vasculitis)
    - > 2 cm with multiple sections reviewed
    - Steroids <2 weeks do not reduce yield and may be sight-saving
- TA u/s, PET, or CT angiography alternative options if biopsy not diagnostic

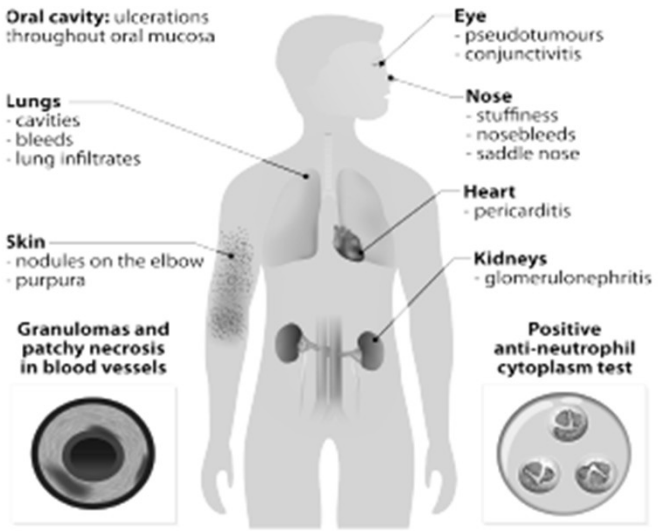



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 2022 ACR/EULAR Criteria for GPA

| Criterion | Points |
|---|---|
| Pos c-ANCA or anti-proteinase 3 | 5 |
| Nasal findings<br>• symptoms (drainage, congestion)<br>• Imaging (consolidations, inflammation) | <br>3<br>1 |
| Cartilaginous abnl (nasal or auricular) | 2 |
| Pulmonary nodules or cavities | 2 |
| Granulomas or giant cells on bx | 2 |
| Pauci-immune glomerulonephritis | 1 |
| Negative points:<br>•Eosinophilia<br>•P-ANCA or anti-myeloperoxidase positivity | <br>Minus 4<br>Minus 1 |

≥5 diagnostic

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

Tuesday, August 25, 2026

41

# Non-AIDS-Defining Complications of HIV/AIDS

Michael Saag, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Non-AIDS-Defining Complications of HIV/AIDS

**Michael Saag, MD**
**University of Alabama at Birmingham**

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Question #1

- 55-year-old man presents with R hip pain
- H/o COPD requiring steroids frequently
- HIV diagnosed 27 years ago
- On TAF / FTC / BIC for 10 years; originally on IND / AZT / 3TC then EFV / TDF/FTC
- Initial HIV RNA 340,000;  CD4 43 cells/ul
  - Now HIV RNA < 50 c/ml;  CD4 385 cells/ul
- Electrolytes NL; Creat 1.3; Phos 3.5 Ca 8.5
- Mg 2.1, alk phos 130; U/A neg
- R Hip film unremarkable

## Question #1

**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



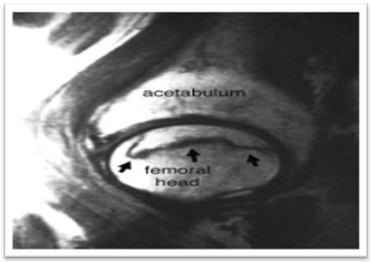
© 2026 Infectious Disease Board Review

## Question #1

### 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

## Osteonecrosis






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

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

## Avascular Necrosis in HIV

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

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

## Question #2

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


© 2026 Infectious Disease Board Review

## Question #2

**Exam**

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

## Question #2

**Labs**

| | | | |
|---|---|---|---|
| 137 | 116 | 5 | Glu 83 |
| 1.6 | 18 | 1.0 | AG 3 |

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

## Question #2

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

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

## Question #2

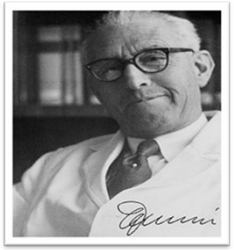
**Which of the following is the most likely diagnosis?**

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


© 2026 Infectious Disease Board Review

## Fanconi's 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



## Question #3

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

## Question #3

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

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

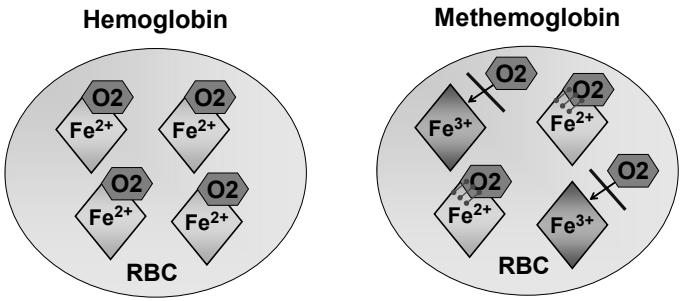
## Question #3

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

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


© 2026 Infectious Disease Board Review

## Hemoglobin and Methemoglobin




## 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

## 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

## 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


© 2026 Infectious Disease Board Review

CLINICAL PRACTICE GUIDELINE

2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

**Recommendation for Persons Living With HIV**
**Referenced studies that support the recommendation are summarized in the Evidence Table.**

| COR | LOE | RECOMMENDATION |
|---|---|---|
| 1 | B-R | 1. In people living with HIV aged 40 to 75 years on stable combination antiretroviral therapy, statin therapy is recommended to reduce risk of a first ASCVD event and reduce the rate of coronary atherosclerosis progression.[1] |

## Question #5

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

## Question #5

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

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

## 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)


© 2026 Infectious Disease Board Review

## Bonus Question #6

**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

## Bonus Question #6

**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

ARV Therapy is 1st Line Rx for HIVAN

## 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

## 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


© 2026 Infectious Disease Board Review

## 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***

## 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)

## 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

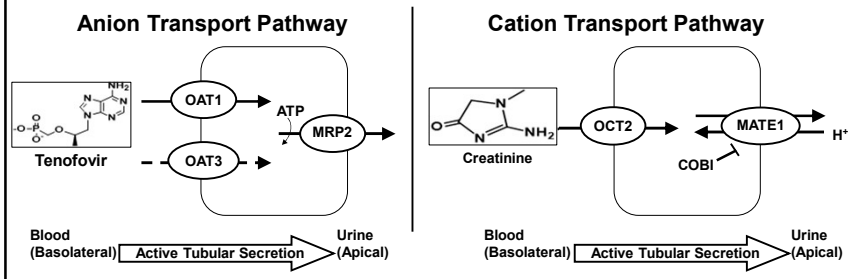
## Question #8

**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


© 2026 Infectious Disease Board Review

## Tenofovir and COBI Interact with Distinct Renal Transport Pathways

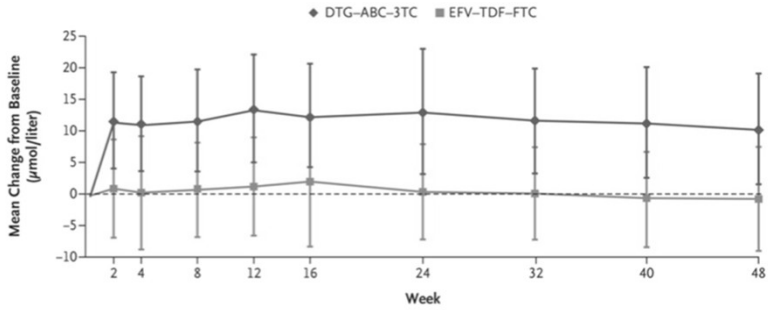



The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

## Changes in eGFR




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

## 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 H20
- Started on TAF/FTC /Bictegravir at week 2
- Returns 6 weeks later, Fever 103 and a mass in supra-clavicular region (3 x 4 cm)

## Question #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


© 2026 Infectious Disease Board Review

## 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

## 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

## 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

## 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

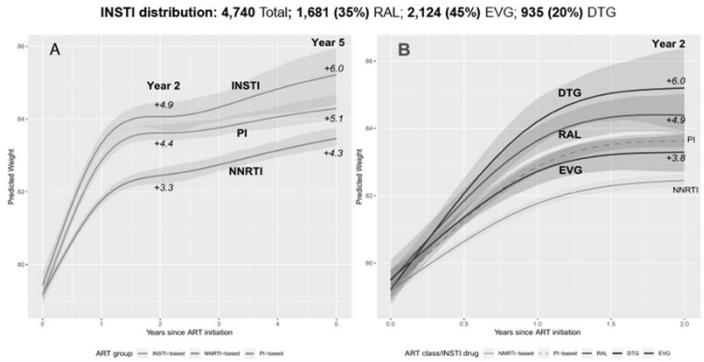

© 2026 Infectious Disease Board Review

## Question #10

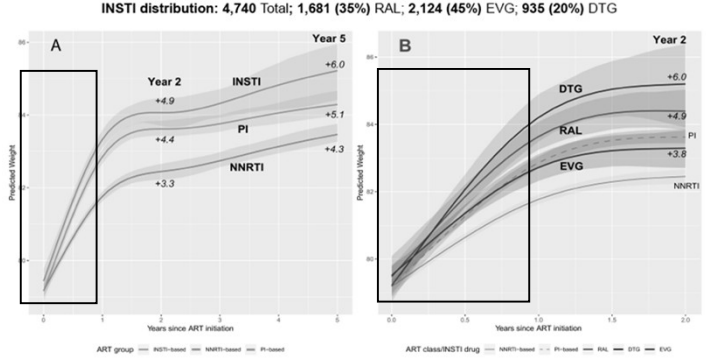
**Which of the following will most likely be present on his 3-month visit from use of dolutegravir?**

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

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

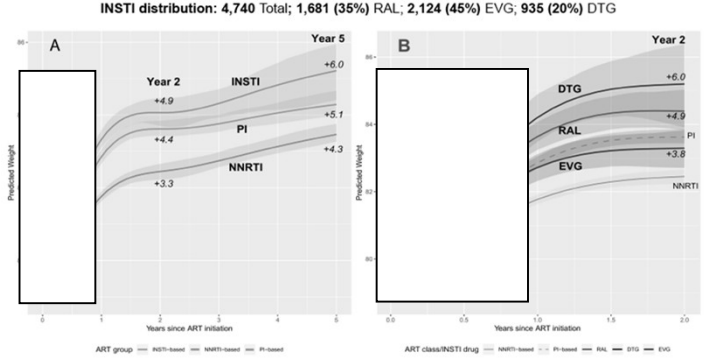



## Change in Weight Overtime – NA-ACCORD Bourgi et al CROI 2019




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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





© 2026 Infectious Disease Board Review

## 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

## Question #11

**Assuming he remains undetectable, what is his risk of transmitting to his seronegative partner through sex?**

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

## Question #11

**Assuming he remains undetectable, what is his risk of transmitting to his seronegative partner through sex?**

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

## PARTNERS Study

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

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


© 2026 Infectious Disease Board Review

## 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

## 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**

## 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

## Question #12

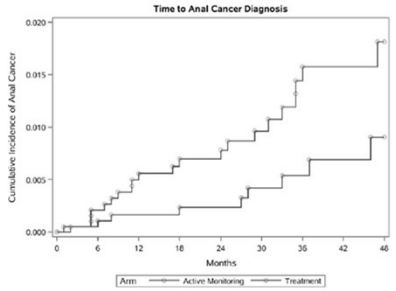
**Which of the following should be performed?**

**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


© 2026 Infectious Disease Board Review

## Treatment Of HSIL Reduces Risk 0of 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)

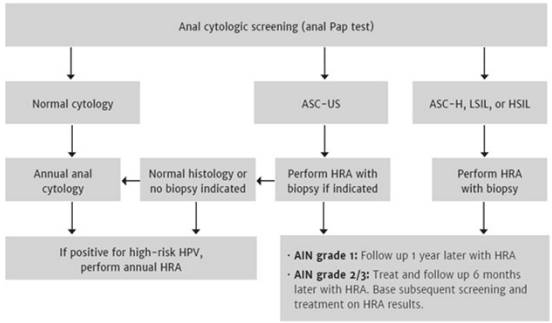



**Anal dysplasia**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

## Figure 1. Follow-up of Anal Cytologic Screening Results




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

NYSDOH AIDS Institute Clinical Guidelines Program

## Recommendations: Screening

CLINICAL GUIDELINES PROGRAM

- 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)

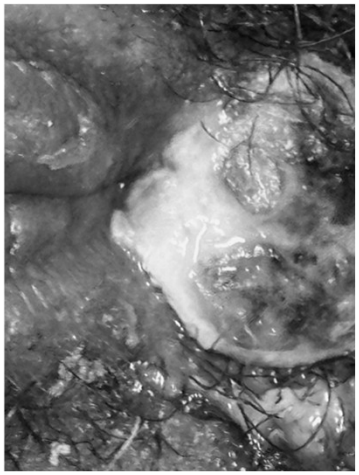
NYSDOH AIDS Institute Clinical Guidelines Program

## 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


© 2026 Infectious Disease Board Review





## 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

## 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***

## Question #14

- 58-year-old man was diagnosed with HIV 25 years ago
- Current Regimen is BIC / TAF / FTC
- His VL has been < 50 c/ml for over 20 years / CD4 count is 540 cells / µl
- He was diagnosed with an aggressive B Cell lymphoma, which failed anthracycline Rx prompting Rx with CAR – T cell infusion
- 6 weeks post-Rx his VL spiked to 1,700 c/ml


© 2026 Infectious Disease Board Review

## Question #14

### What is the most likely cause of his HIV viremia?

A. ARV medication non-adherence
B. Drug-Drug interaction with chemotherapy
C. False positive VL test
D. Poor absorption of ARV medication owing to divalent cations
E. Superinfection with an HIV resistant strain
F. Radiation exposure from bombing an Iranian Nuclear facility

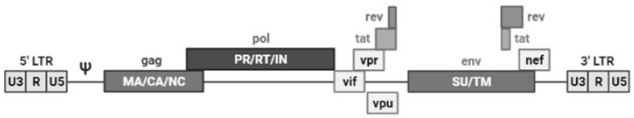
## Question #14

### What is the most likely cause of his HIV viremia?

A. ARV medication non-adherence
B. Drug-Drug interaction with chemotherapy
**C. False positive VL test***
D. Poor absorption of ARV medication owing to divalent cations
E. Superinfection with an HIV resistant strain
F. Radiation exposure from bombing an Iranian Nuclear facility

## False Positive VL Test

- CAR-T cell Rx uses a lentivirus vector, rich in LTR fragments to transduce T-cells with receptor target genes
- Roche COBAS / Amplicor HIV RNA assay targets 5' LTR as a conserved region of HIV




- Abbott Real Time HIV-1 VL targets the pol gene and can be used

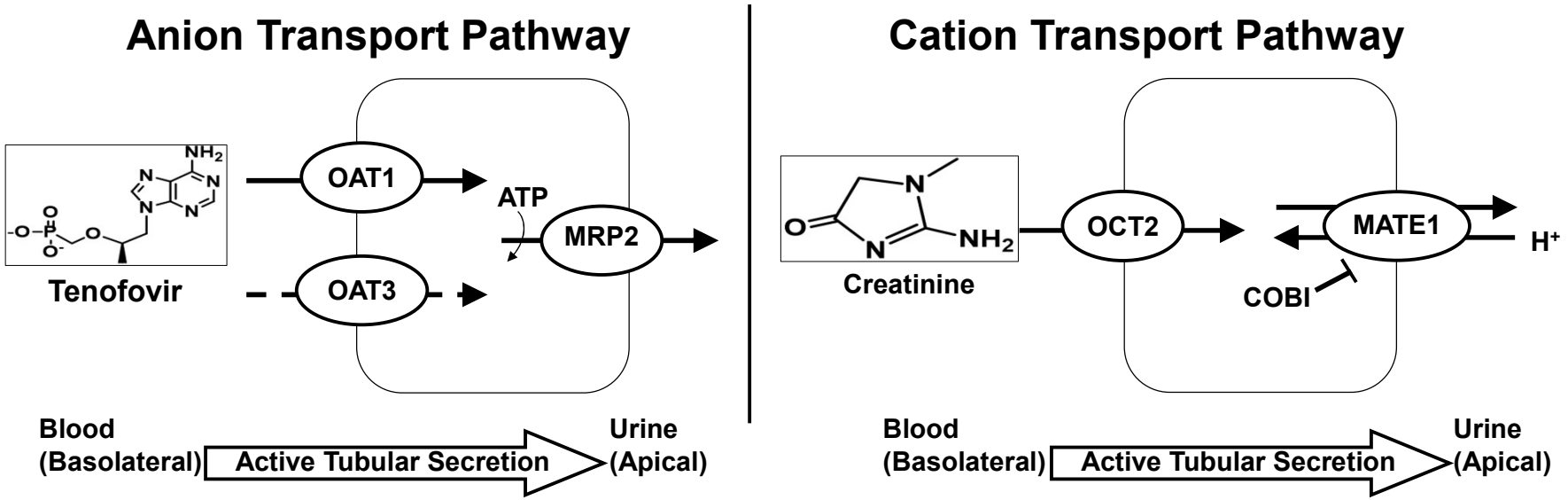
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**msaag@uabmc.edu**



© 2026 Infectious Disease Board Review

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

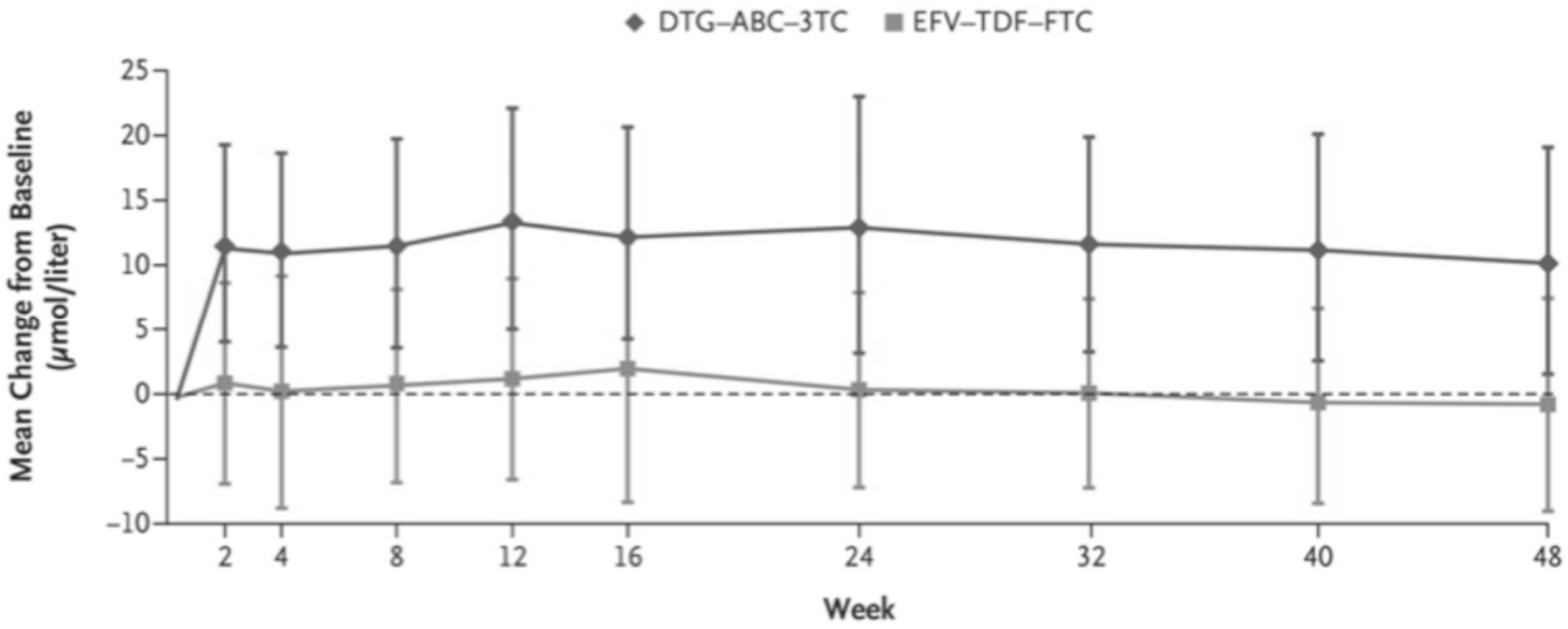

Ray A, et al. Antimicro Agents Chemo 2006;3297-3304
Lepist E, et al. ICAAC 2011; Chicago. #A1-1724





© 2026 Infectious Disease Board Review

# Changes in eGFR




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

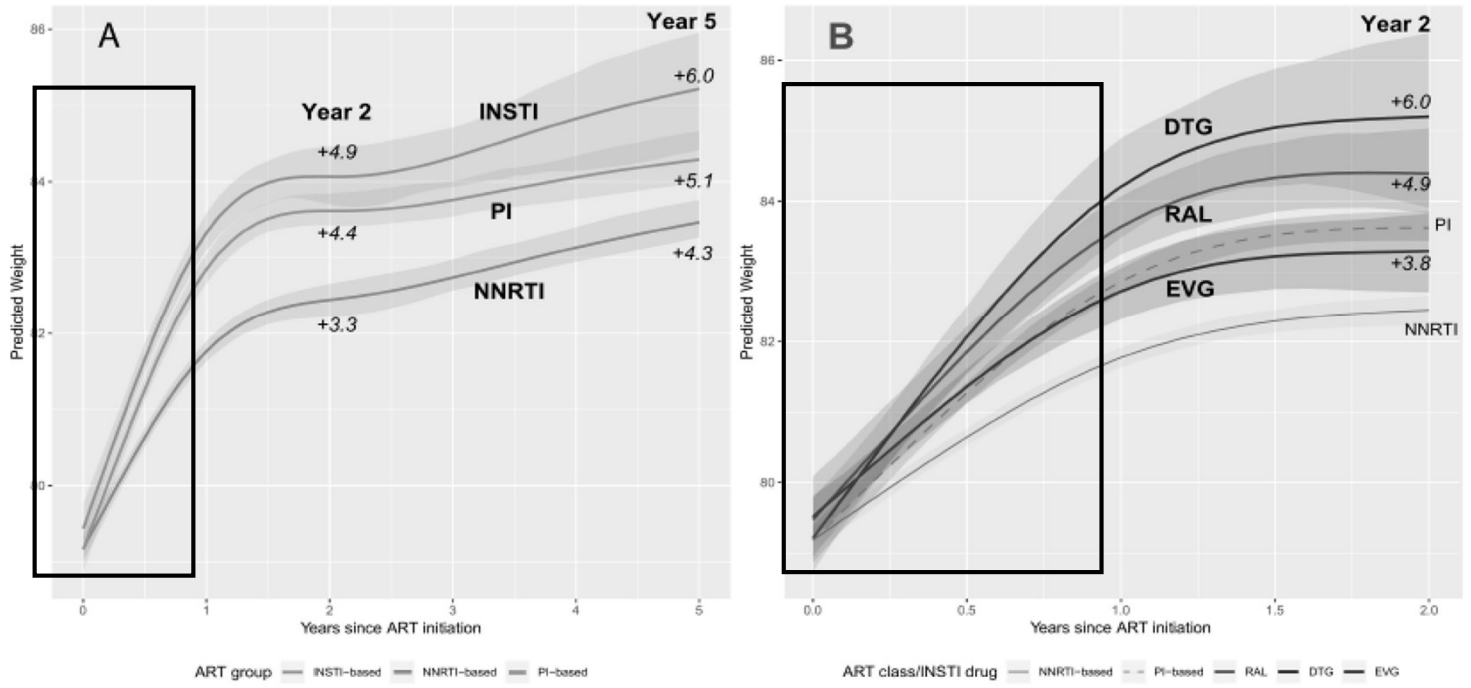
Walmsley, et al. N Engl J Med. 2013;369:1807-18.



© 2026 Infectious Disease Board Review

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

**INSTI distribution: 4,740** Total; **1,681 (35%)** RAL; **2,124 (45%)** EVG; **935 (20%)** DTG




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

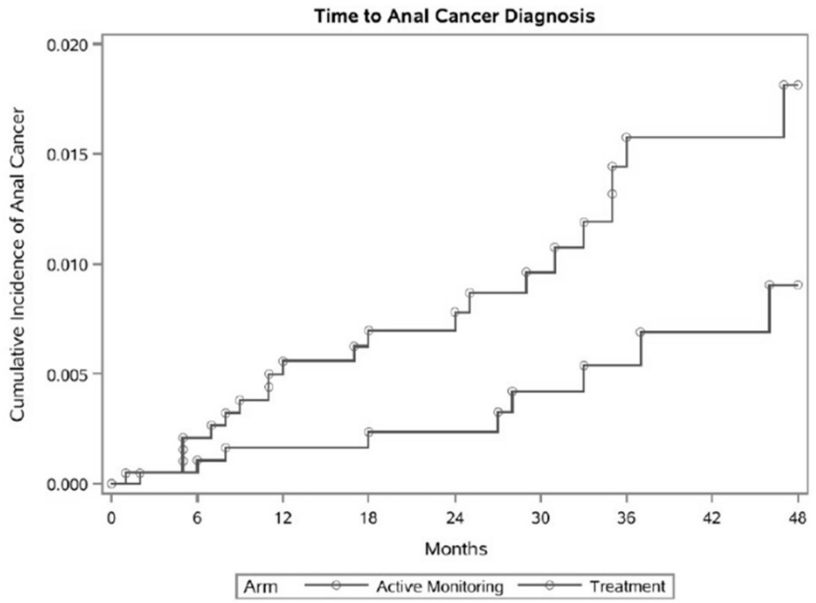


© 2026 Infectious Disease Board Review

# Treatment Of HSIL Reduces Risk 0of 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**



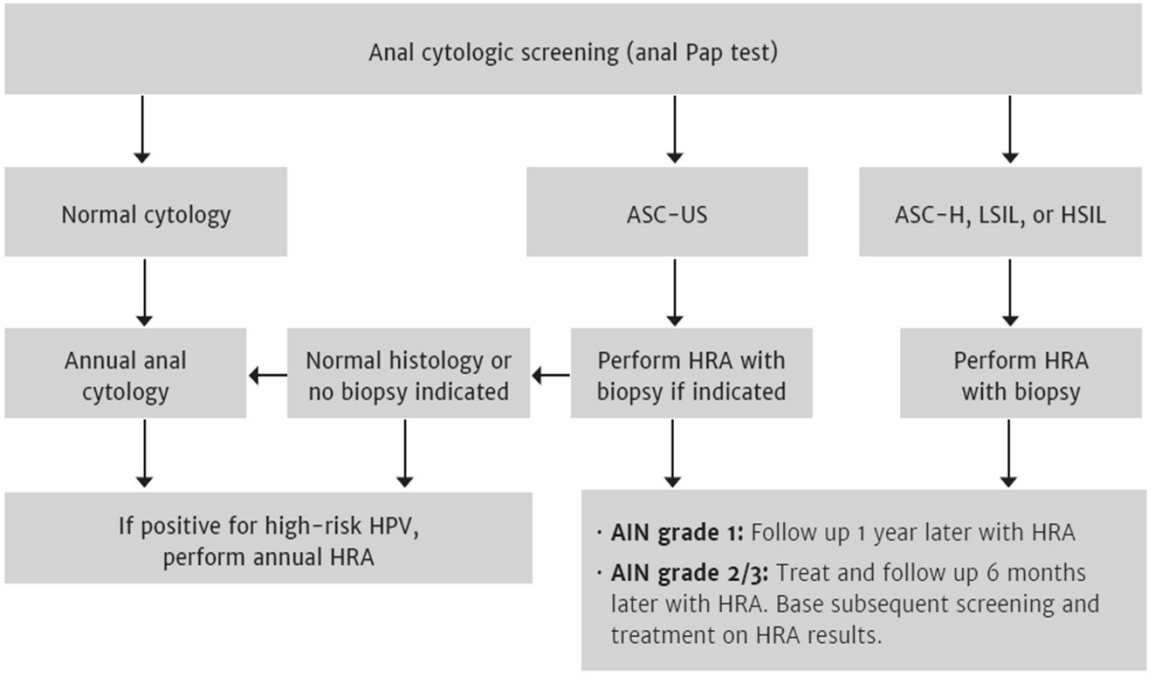

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



© 2026 Infectious Disease Board Review

# Figure 1. Follow-up of Anal Cytologic Screening Results




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

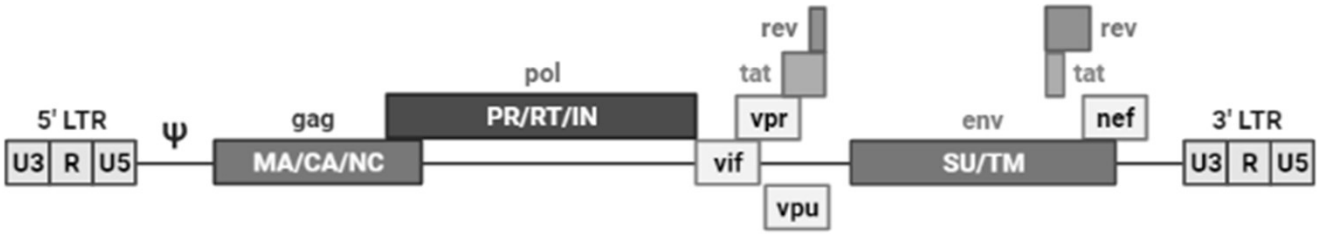
NYSDOH AIDS Institute Clinical Guidelines Program



© 2026 Infectious Disease Board Review

# False Positive VL Test

- CAR-T cell Rx uses a lentivirus vector, rich in LTR fragments to transduce T-cells with receptor target genes
- Roche COBAS / Amplicor HIV RNA assay targets 5’ LTR as a conserved region of HIV




- Abbott Real Time HIV-1 VL targets the pol gene and can be used

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**42**

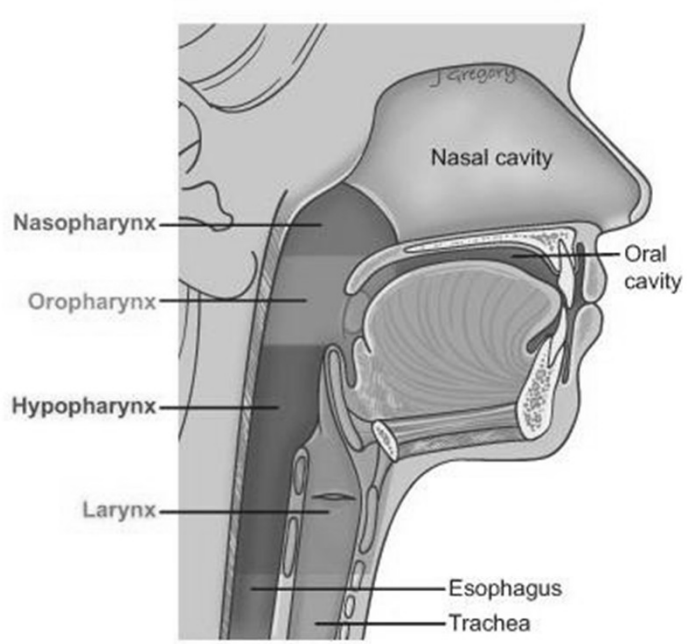
# Pharyngitis Syndromes Including Group A Strep Pharyngitis

**Karen Bloch, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Pharyngitis




- Micro-neighborhoods
- Regional differences

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 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% |

2025 IDSA guidelines recommend:

- Clinical scoring systems are most useful in identifying low-risk patients who don't require testing
- High-risk individuals should be tested even in low scores
  - Exposure to household contact
  - Prior RF
  - Signs or symptoms of iGAS

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Pharyngitis & Rash

- Acute HIV

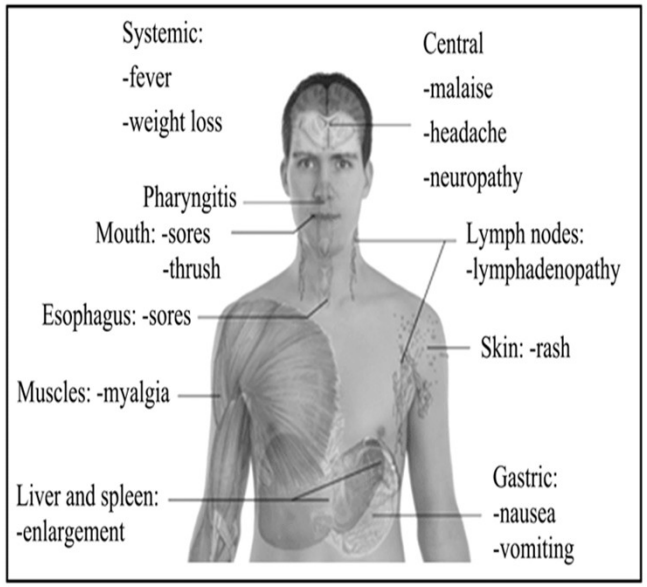



Figure 1 Main symptoms of acute HIV infection

- Secondary syphilis



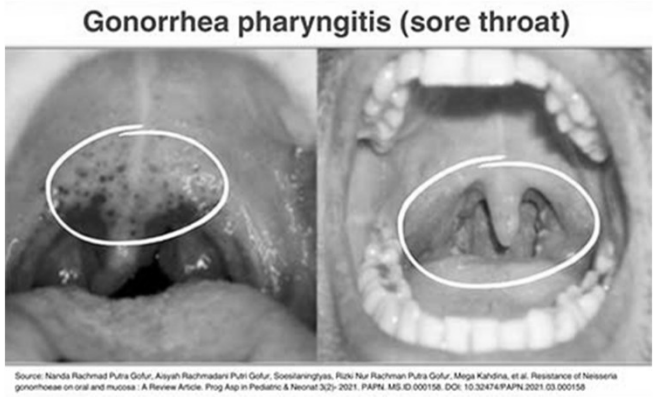
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Pharyngitis after Receptive Oral Intercourse

## *Neisseria gonorrhoeae*

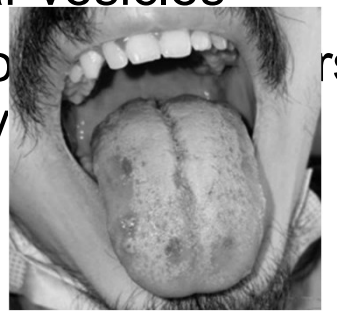
- Highest risk MSM
- Often asymptomatic




Source: Nanda Rachmad Putra Gofur, Aisyah Rachmadani Putri Gofur, Soesilaningtyas, Rizki Nur Rachman Putra Gofur, Mega Kahdina, et al. Resistance of Neisseria gonorrhoeae on oral and mucosa : A Review Article. Prog Asp in Pediatric & Neonat 3(2)- 2021. PAPN. MS.ID.000158. DOI: 10.32474/PAPN.2021.03.000158

## Herpes Simplex Virus

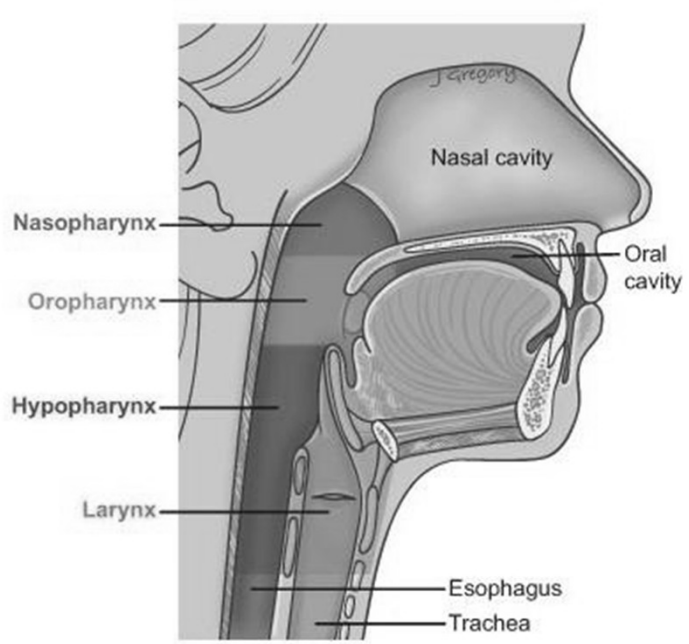
- HSV-1 or HSV-2
- Usually with initial infection
- Tonsillar vesicles
- Labial o rs variably



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Pharyngitis




- Micro-neighborhoods
- Regional differences

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# 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% |

2025 IDSA guidelines recommend:

- Clinical scoring systems are most useful in identifying low-risk patients who don't require testing
- High-risk individuals should be tested even in low scores
  - Exposure to household contact
  - Prior RF
  - Signs or symptoms of iGAS

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Pharyngitis & Rash

- Acute HIV

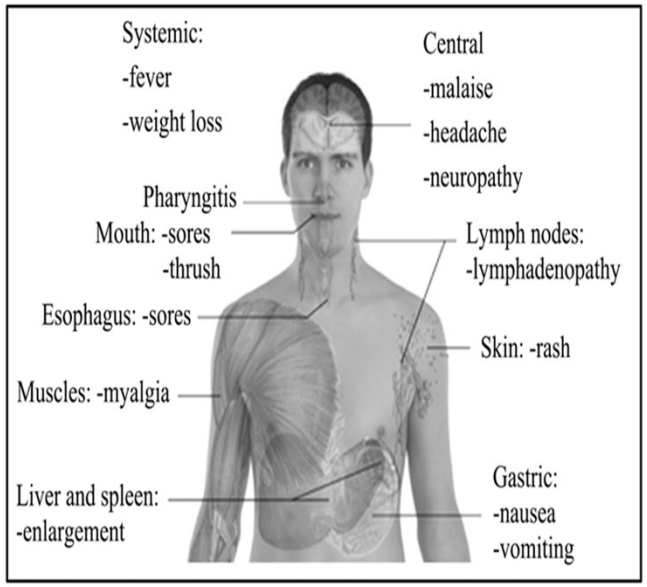



Figure 1 Main symptoms of acute HIV infection

- Secondary syphilis



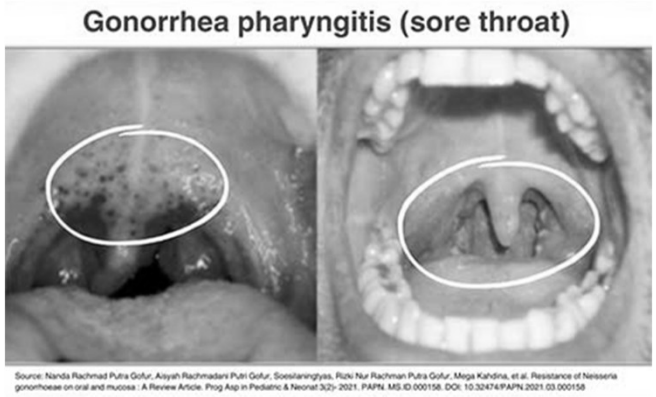
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Pharyngitis after Receptive Oral Intercourse

## *Neisseria gonorrhoeae*

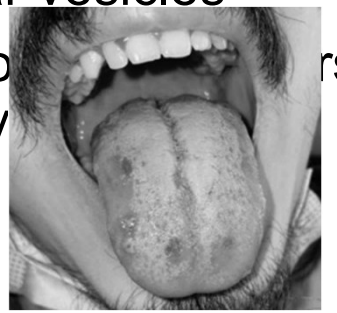
- Highest risk MSM
- Often asymptomatic




Source: Nanda Rachmad Putra Gofur, Aisyah Rachmadani Putri Gofur, Soesilaningtyas, Rizki Nur Rachman Putra Gofur, Mega Kahdina, et al. Resistance of Neisseria gonorrhoeae on oral and mucosa : A Review Article. Prog Asp in Pediatric & Neonat 3(2)- 2021. PAPN. MS.ID.000158. DOI: 10.32474/PAPN.2021.03.000158

## Herpes Simplex Virus

- HSV-1 or HSV-2
- Usually with initial infection
- Tonsillar vesicles
- Labial o rs variably



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

**Tuesday, August 25, 2026**

---

**43**

# Herpes Simplex

**Richard Whitley, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# 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

9/7/2026



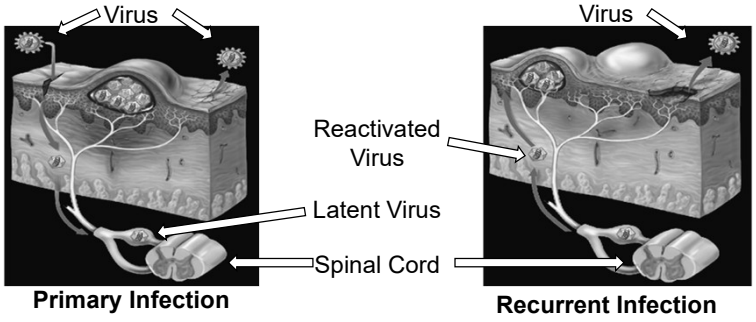

## Disclosures of Financial Relationships with Relevant Commercial Interests

- Steering Committee: NIAID COVID-19 Recover, Recover VITAL Study
- Scientific Advisory Board: Treovir, LLC
- Scientific Advisory Board: Altesa Biosciences
- Member, Board of Directors, Evrys Bio
- Member, Board of Directors, Virios Therapeutics
- Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB

## Herpes Viruses: The Family

- **Herpes simplex virus, type 1 (HSV-1)**
- **Herpes simplex virus, type 2 (HSV-2)**
- **Varicella zoster virus (VZV)**
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

## Viral Latency and Reactivation



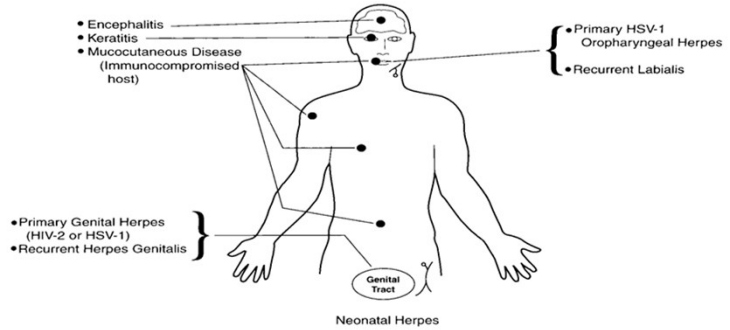

Netter FH. ©2001 by Icon Learning Systems

**43 Herpes Simplex and Varicella Zoster**

*Speaker: Richard Whitley, MD*

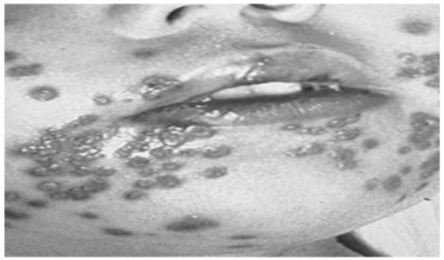
© 2026 Infectious Disease Board Review

## Clinical Manifestations of Herpes Simplex Virus Infections

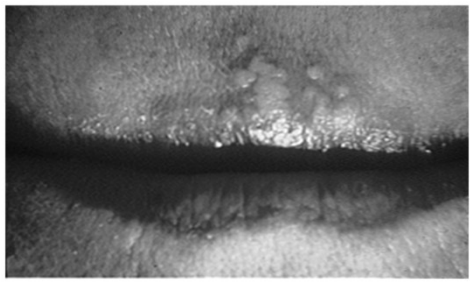



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Primary Herpes Simplex Virus Infection: Cutaneous Lesions



## Herpes Simplex Labialis



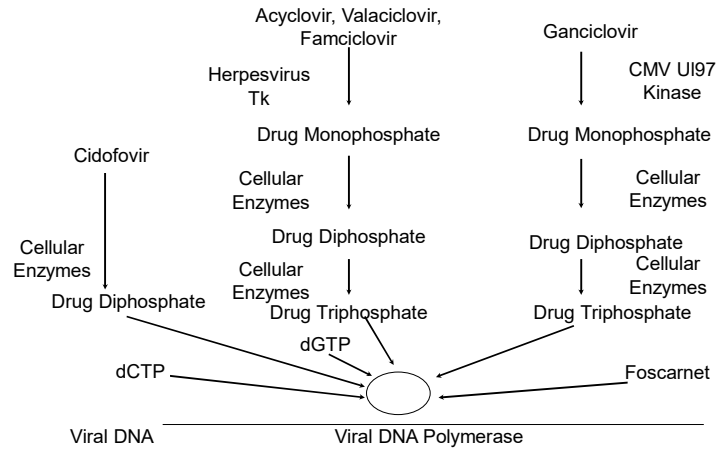
## Immunocompromised Host




© 2026 Infectious Disease Board Review

## Most Widely Used Systemic Anti-HSV and VZV Drugs

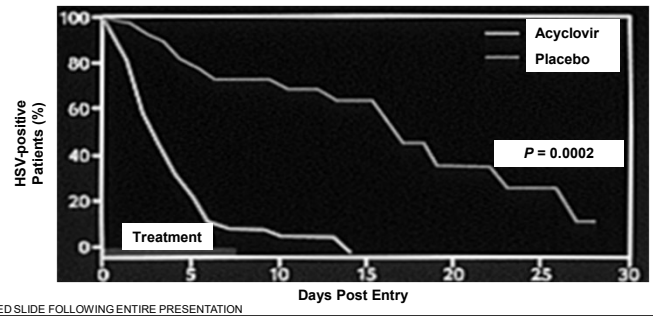
- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

Time To Cessation of Viral Shedding with Acyclovir



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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 | |


© 2026 Infectious Disease Board Review



## Question #1

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

**What is the most likely cause for disease progression regarding a deficiency or alteration?**

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

## Question #1

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

**What is the most likely cause for disease progression regarding a deficiency or alteration?**

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

## 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


© 2026 Infectious Disease Board Review

## 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***

## Answers 1 and 2

- Three types of acyclovir resistant viruses:
  - Thymidine kinase negative
  - Thymidine kinase altered substrate
  - DNA polymerase mutations
- All populations of HSV contain viruses with resistant genotypes
- Progressive disease has been limited to the immunocompromised host, especially HSCT recipients and those with poorly controlled HIV
- Three normal hosts with documented ACV resistant virus had disease progression

## 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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Acyclovir Therapy of Genital Herpes

**Summary of clinical benefit for treatment of:**

- Primary
- Recurrent
- Suppressive

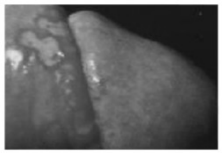


© 2026 Infectious Disease Board Review

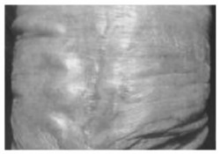
## Spectrum of HSV Clinical Presentation



First Infection

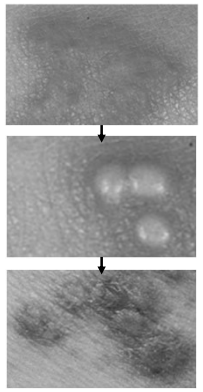


Classical Recurrence



Atypical Recurrence

## Progression of Lesions



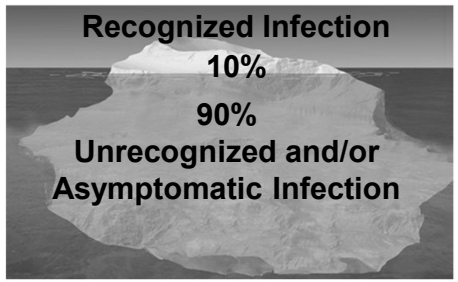
Early Redness/Swelling

Thin-Walled Fluid-Filled Vesicles and Pustules

Early Healing of Vesicles, Erosions, or Ulcers

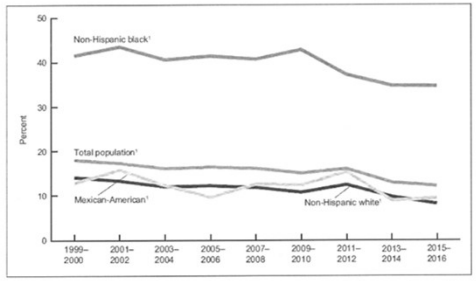
## Clinical Spectrum of HSV-2

HSV-2 Seroprevalence




Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839

## HSV-2 seroprevalence has decreased over time, overall and in all racial/ethnic groups




¹ Significant decreasing linear trend over time, p<0.05
NOTES: Age adjusted by the direct method to the 2000 US Census population, using age groups 14-19, 20-29, 30-39, and 40-49 years. Total population includes all race and Hispanic origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population.

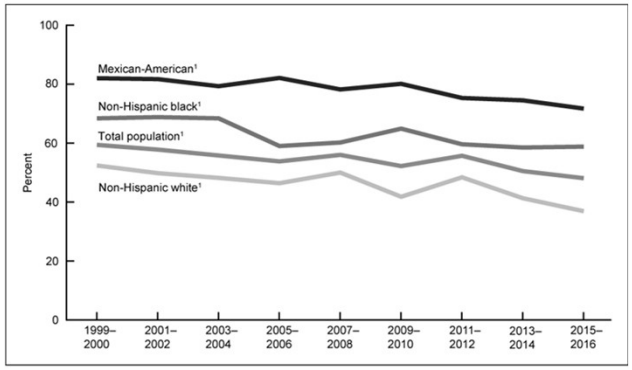
McQuillan, et al. NCHS Data Brief 2018.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

Figure 2. Trends in age-adjusted prevalence of herpes simplex virus type 1 among persons aged 14–49, for the total population and by race and Hispanic origin: United States, 1999–2000 through 2015–2016

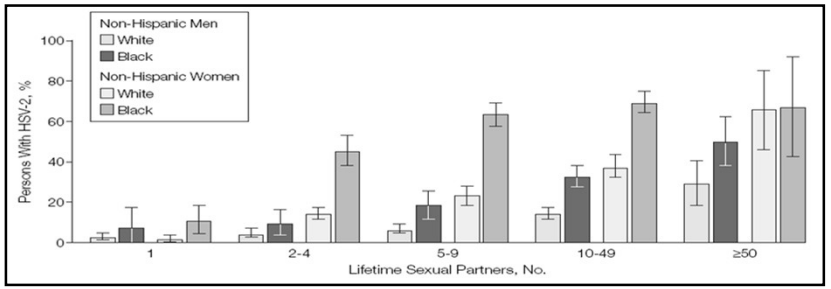



¹Significant decreasing linear trend over time, $p < 0.05$.
NOTES: Age adjusted by the direct method to the 2000 U.S. Census population, using age groups 14–19, 20–29, 30–39, and 40–49 years. Total population includes all race and Hispanic-origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db304_table.pdf#2.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

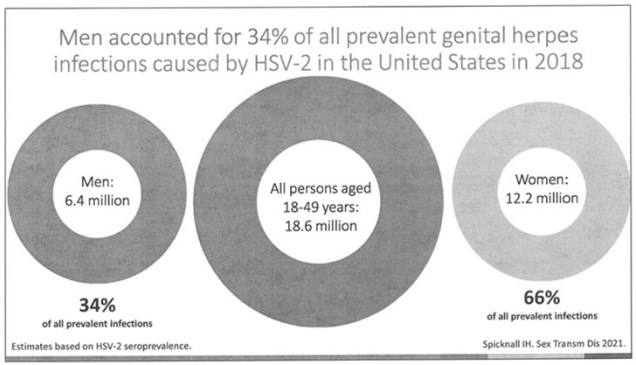
## Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence

**According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004**

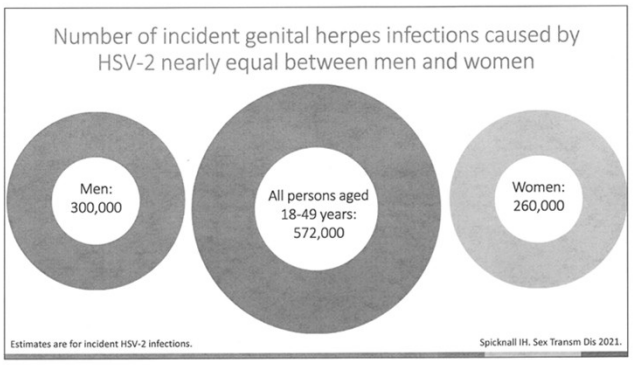



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

JAMA, August 23/30, 2006 Vol 296 No 8 pg 967




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

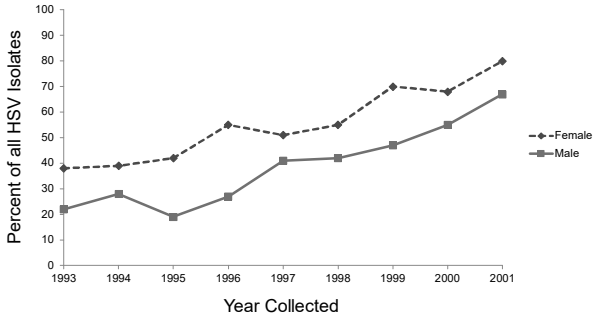
## Genital Herpes
### Transmission

Men — Asymptomatic Recurrence → Women

Women — Transmission
- Symptomatic Recurrence → 30%
- 70%

Corey L. *Sex Transm Dis*. 1994;21(S38-S44
Mertz GJ, et al. *Ann Intern Med*. 1992;116:197-202

## HSV-1 Genital Isolates Among U.S. College Students

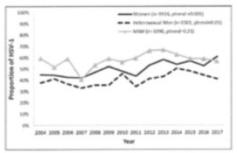



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Sex Transm Dis 2003;30:797-800

## 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**

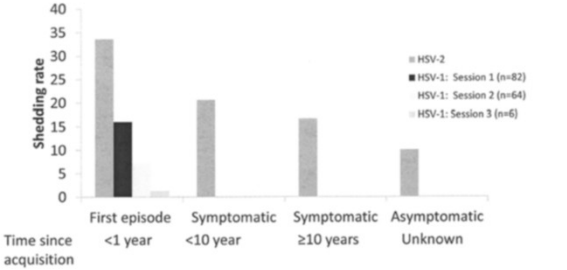



Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Genital Shedding Rate: HSV-2 vs. HSV-1




Johnston et al, ISSTDR 2019
Phipps et al, JID 2011
Tronstein et al, JAMA 2011

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

## Genital Herpes
### Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

*Genital Herpes – A Clinician's Guide to Diagnosis and Treatment.* American Medical Association. 2001:1-20.
Whitley RJ, et al. *Clin Infect Dis.* 1998;26:541-555.

## Herpes Presenting as Ulceration

The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.

**What is the key to the diagnosis?**

A. The fact that lesions recurred
B. Site of involvement is not unusual
C. Trauma can induce reactivation



Photo courtesy of Jeffrey Gilbert, MD

## Question #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

## 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***

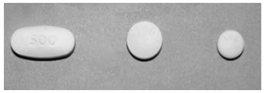

© 2026 Infectious Disease Board Review

## Answer #3

- Historically, culture of HSV was the gold standard. Using daily cultures to detect viral shedding resulted in 4-7% of all days being positive.
- Use of PCR has replaced culture and detects shedding in up to ~25% of days. More recent data show intermittent shedding on the same day.
- A culture isolate of virus is required to test for resistance
- Serology can be used to assess prior exposure to HSV. The distinction between HSV glycoprotein 1 and 2 is best performed by Western Blot (U. Washington).

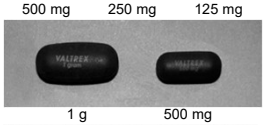
## Oral Antiviral Therapies

- **Famciclovir [Famvir®]**



500 mg 250 mg 125 mg

- **Valaciclovir [Valtrex®]**



1 g 500 mg

- **Acyclovir [Zovirax®]**



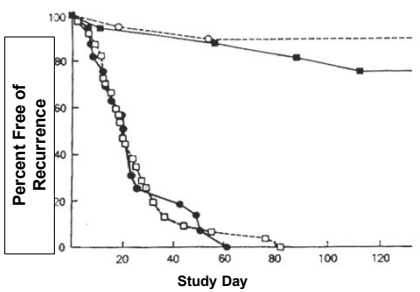
800 mg 600 mg 200 mg

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline

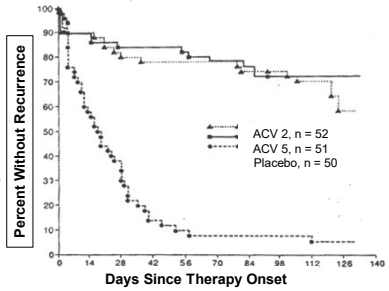
## Impact of Acyclovir Therapy on Primary Genital HSV Infection

| | Treatment Group (Days) | | | |
|---|---|---|---|---|
| | **Acyclovir** | **Placebo** | **RR** | **P** |
| Virus Shedding | **2.8** | **16.8** | **6.82** | **0.0002** |
| Pain | **8.9** | **13.1** | **2.00** | **0.01** |
| Scabbing | **9.3** | **13.5** | **2.21** | **0.004** |
| Healing | **13.7** | **20.1** | **1.83** | **0.04** |

## Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes




Straus, et al. *NEJM*, 1984




Douglas, et al, *NEJM*, 1984

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

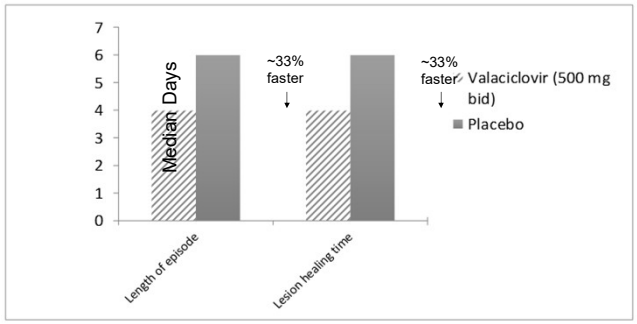
## Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

## Acyclovir/Valacyclovir Kinetics

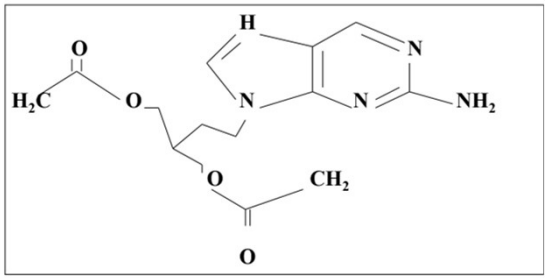
| Drug | Dose | Pharmacokinetics | |
|---|---|---|---|
| | | $C_{max}$ (μg/mL) | Daily AUC (μg/mL•h) |
| VALTREX | 1 g 3x/d | 5.0 | 47 |
| Oral ZOVIRAX | 800 mg 5x/d | 1.6 | 24 |
| IV ZOVIRAX | 5 mg/kg 3x/d | 9.8 | 54 |
| | 10 mg/kg 3x/d | 20.7 | 107 |

## Therapy of Recurrent Genital Herpes
### Duration of Disease




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

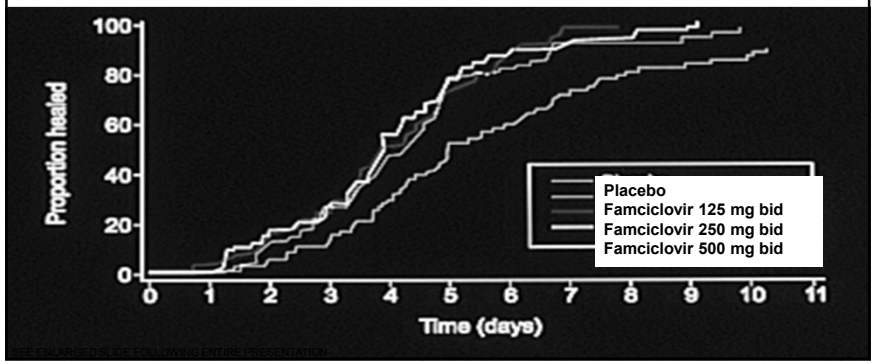
## Famciclovir





© 2026 Infectious Disease Board Review

## Famciclovir Therapy of Recurrent Genital Herpes




## Shorter and Shorter Therapy

- **Genital Herpes**
  - Valacyclovir: three days
  - Famciclovir: one day
- **Labial Herpes**
  - Valacyclovir: two days
  - Famciclovir: one day

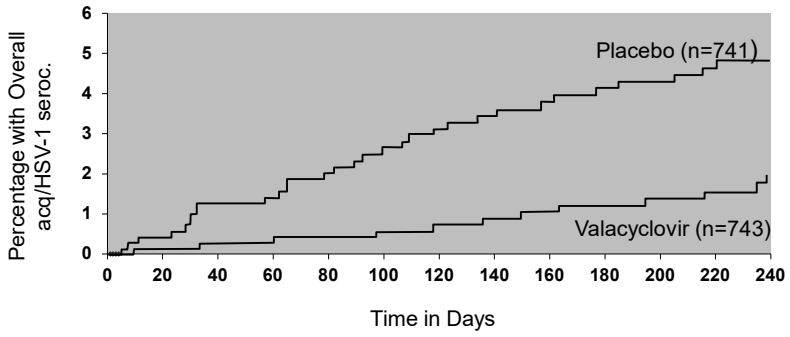
## Prevention of Person-to-Person Transmission

## Valacyclovir Prevention of HSV Transmission to Susceptible Partners

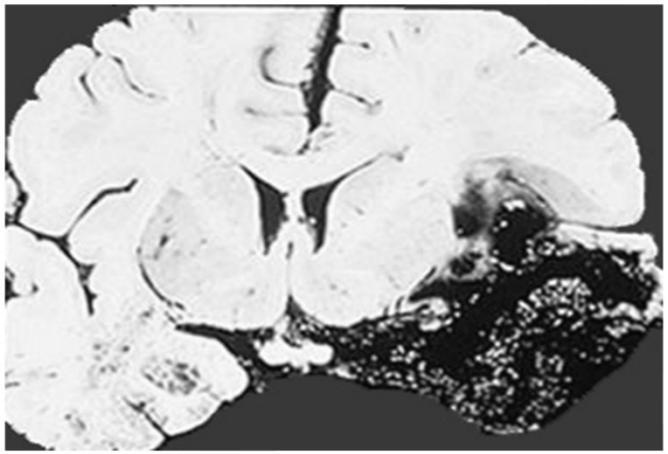
| Susceptible Partner | Val-ACV N = 743 | Placebo N = 741 | Total |
|---|---|---|---|
| No. acquired HSV-2 | 14 | 28 | 42 |
| No. acquired HSV-1 | 0 | 4 | 4 |
| No. developed clinical HSV-2 | 4 | 17 | 21 |


© 2026 Infectious Disease Board Review

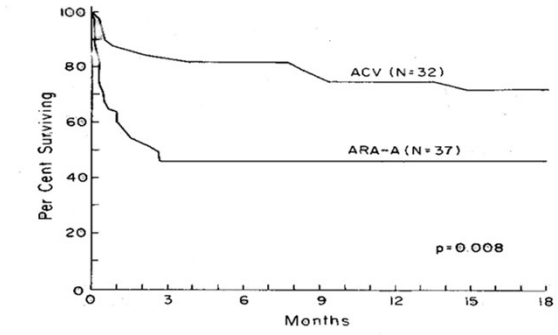
## Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



## Herpes Simplex Encephalitis Survival




**Vidarabine (ARA-A)**
**Vs.**
**Acyclovir (ACV);**
**P=0.008**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## HSE Morbidity

**Percent Patients**
**Patient Normal/Mild Impairment**

| Age | Glasgow Coma Scale | |
|---|---|---|
| | <6 | >6 |
| <30 | 0 | 30 |
| <30 | 0 | 36 |



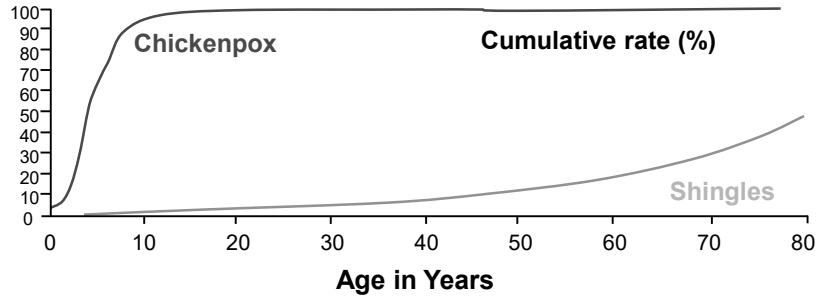
© 2026 Infectious Disease Board Review

## Sensitivity and Specificity of PCR

| | Biopsy Positive | Biopsy Negative |
|---|---|---|
| PCR Positive | 53 | 3 |
| PCR Negative | 1 | 44 |

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

## Varicella Zoster Virus Infection




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

## Chicken Pox: Is Therapy of Value?

## Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

| | Acyclovir (n=38) | Placebo (n= 38) | *P* |
|---|---|---|---|
| Time to maximum number of skin lesions (days) | 1.5 | 2.1 | 0.002 |
| Days of new lesion information | 2.7 | 3.3 | 0.03 |
| Time to onset of cutaneous healing (days) | 2.6 | 3.3 | <0.001 |
| Time to 100% crusting (days) | 5.6 | 7.4 | 0.001 |
| Maximum number of lesions | 268 | 500 | 0.04 |



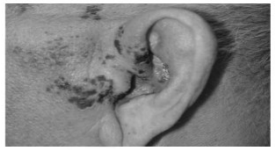
© 2026 Infectious Disease Board Review

## Thoracic Herpes Zoster



## Questions

- What is the most likely diagnosis?
- How would you prove the etiology?



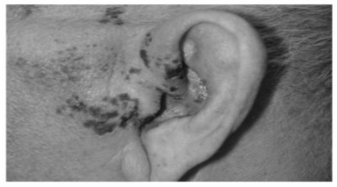
## Answer

- 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.

## Question #4

**What complication would you be most concerned about?**

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies



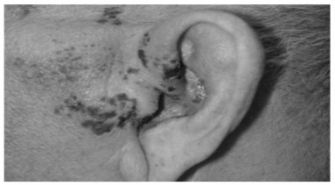
http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html


© 2026 Infectious Disease Board Review

## 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

## 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.

## 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?

**What complication is it most likely to be associated with this illness?**

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke



www.medscape.com

## 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?

**What complication is it most likely to be associated with this illness?**

A. Deafness
B. Vertigo
C. Optic neuritis
**D. Keratitis***
E. Stroke



www.medscape.com



© 2026 Infectious Disease Board Review

## Answer #5

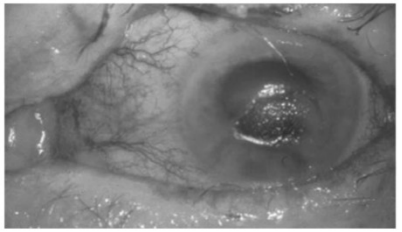
- This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e., ophthalmic branch of the trigeminal nerve, which innervates the tip of the nose and the globe. After a prodrome of fever and headache for 1-4 days, patients develop a cutaneous rash. Days or up to 3 weeks later, 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.

## Hutchison's Sign

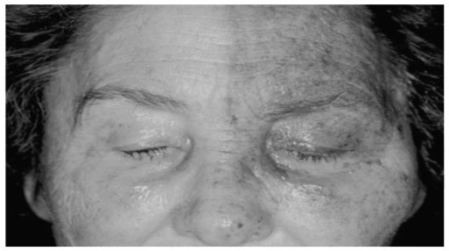
**Zoster Involving Nasociliary Branch, Cranial Nerve VII Which Innervates the Tip of the Nose and the Cornea**







## Zoster Ophthalmicus



## Natural History of Zoster in the Normal Host

- Acute neuritis may precede rash by 48 - 72 hours
- Maculopapular eruption, followed by clusters of vesicles
- Unilateral dermatomal distribution


© 2026 Infectious Disease Board Review

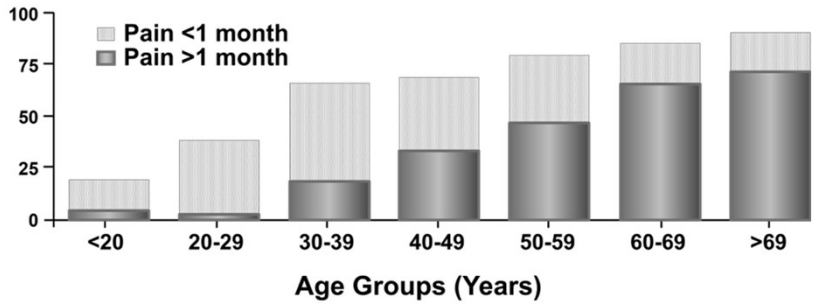
## Natural History of Zoster in the Normal Host

- Events of healing:
  - **Cessation of new vesicle formation:** **3 - 5 days**
  - **Total pustulation:** **4 - 6 days**
  - **Total scabbing:** **7 - 10 days**
  - **Complete healing** **2 - 4 weeks**
- Cutaneous dissemination can occur dissemination is extremely rare
- Postherpetic neuralgia in 10% - 40% of cases

## Complications of Zoster

| Common | Uncommon |
|---|---|
| • Postherpetic neuralgia | • 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) |

## Prevalence and Duration of Pain



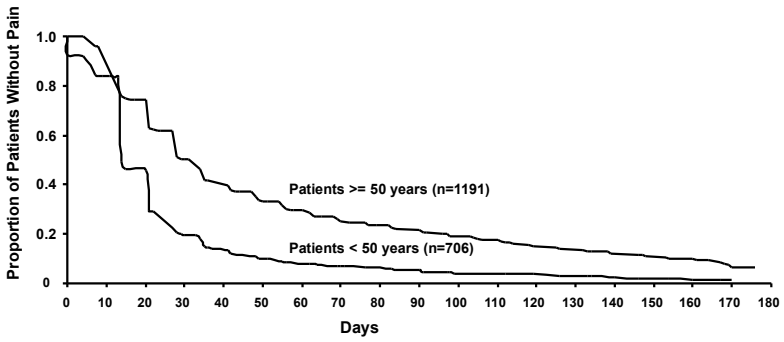

de Moragas et al. *Arch Derm.* 1957;75:193-196

## Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

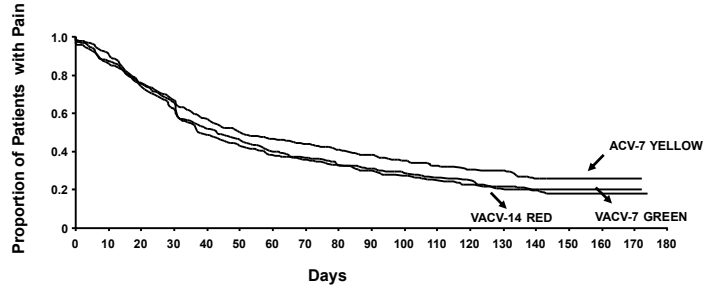

© 2026 Infectious Disease Board Review

## Time to Cessation of Zoster Associated Pain




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

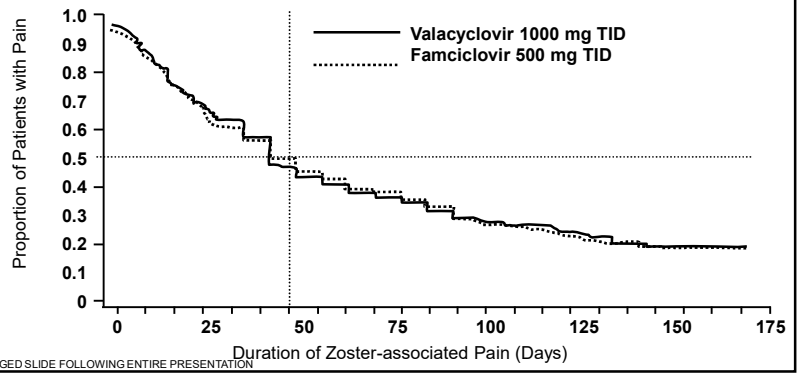
## Time to Cessation of Zoster Associated Pain n=1141




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

## Resolution of Pain in Herpes Zoster with Valacyclovir and Famciclovir




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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


© 2026 Infectious Disease Board Review

## Question #6

**What is the most likely etiologic agent?**

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6



www.cdc.gov

## Question #6

**What is the most likely etiologic agent?**

**A. HSV***
B. VZV
C. CMV
D. EBV
E. HHV6



www.cdc.gov

## Answer #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.

## 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)


© 2026 Infectious Disease Board Review

## 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

Teaser: Vaccine is associated with decreased occurrence of Alzheimer's disease

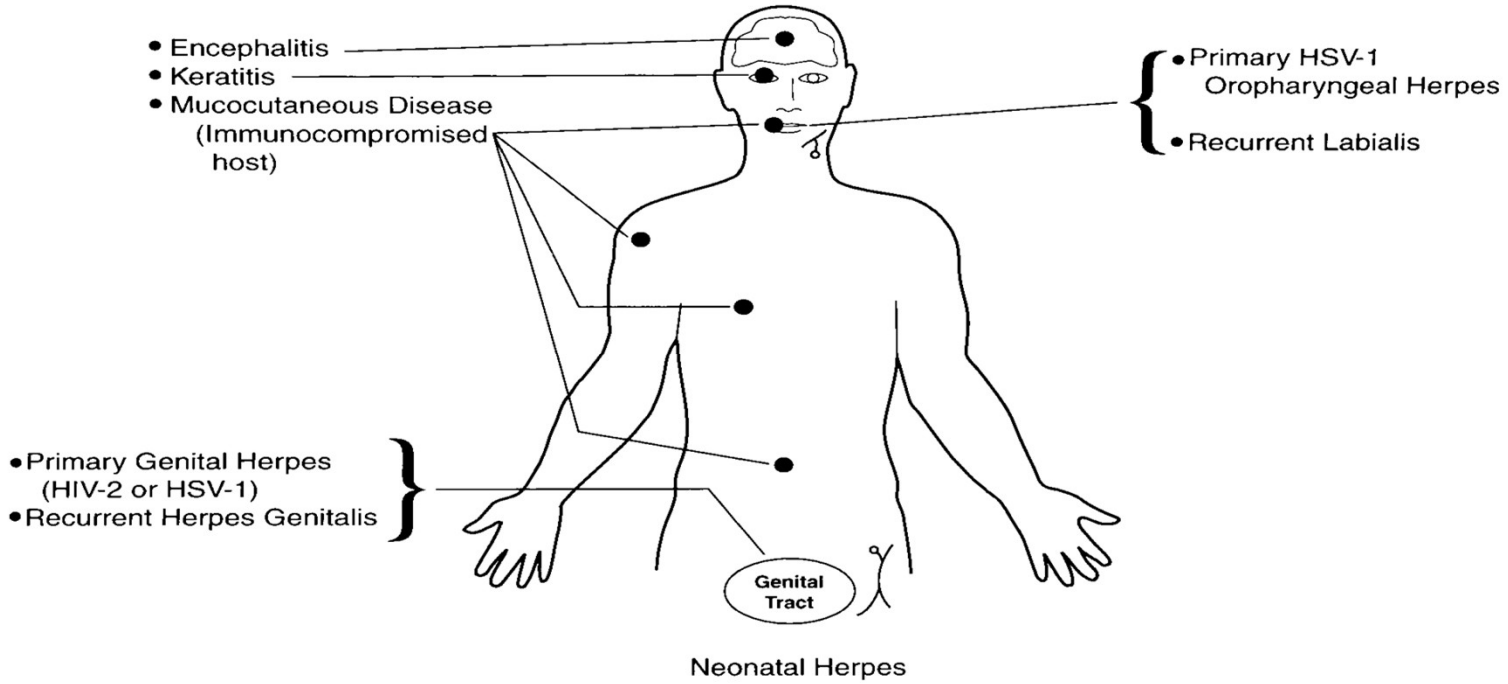
**Thank You**

**rwhitley@uabmc.edu**



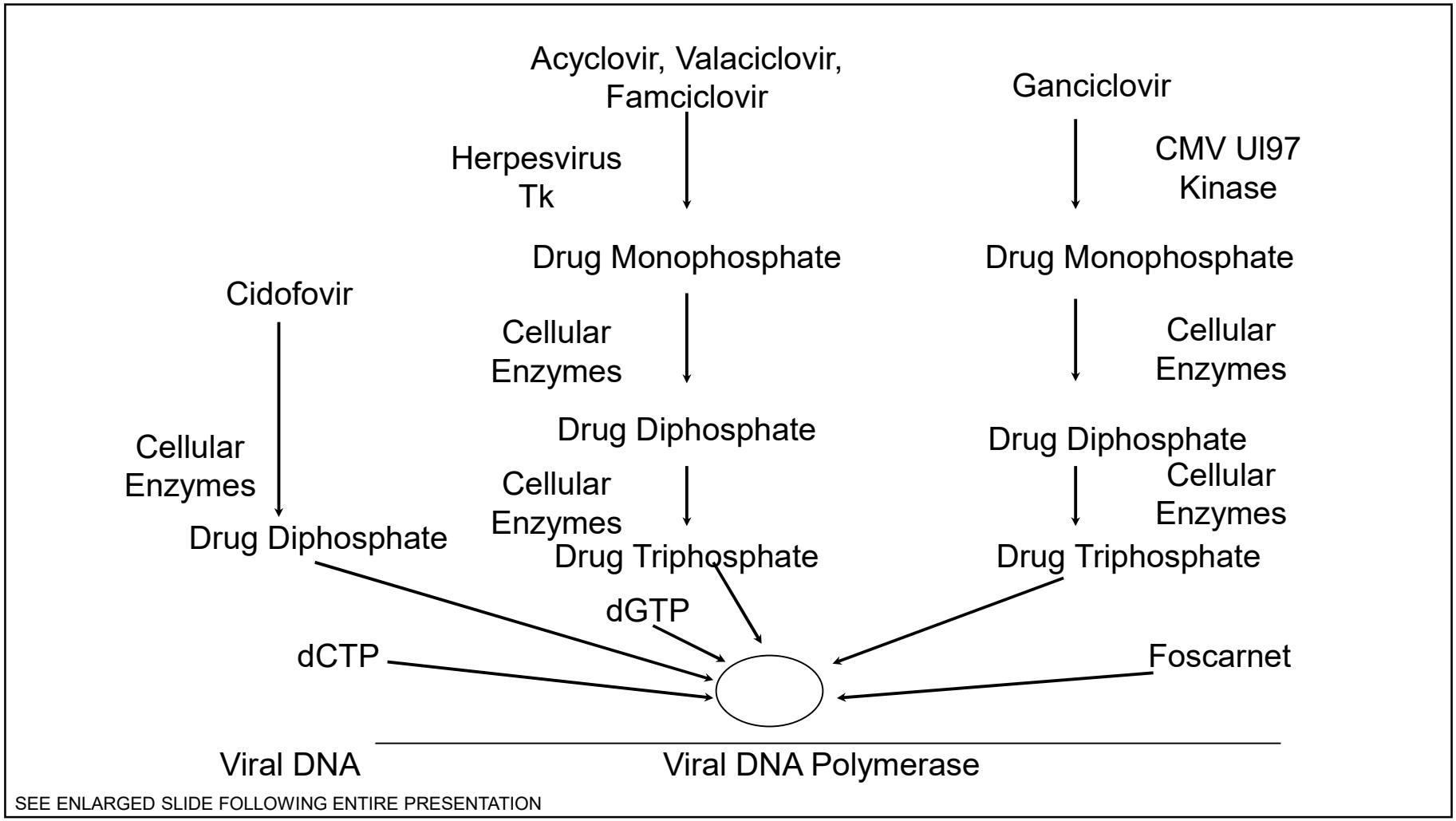
© 2026 Infectious Disease Board Review

# Clinical Manifestations of Herpes Simplex Virus Infections




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

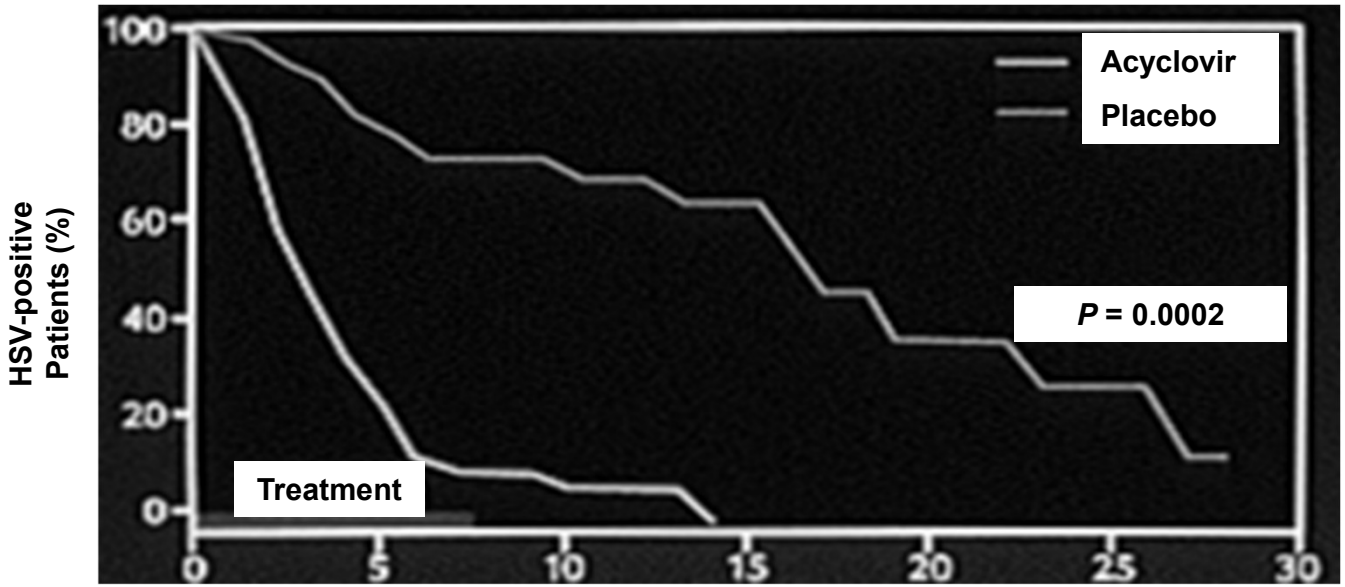



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

## Time To Cessation of Viral Shedding with Acyclovir




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Global Prevalence of HSV-2 Infection



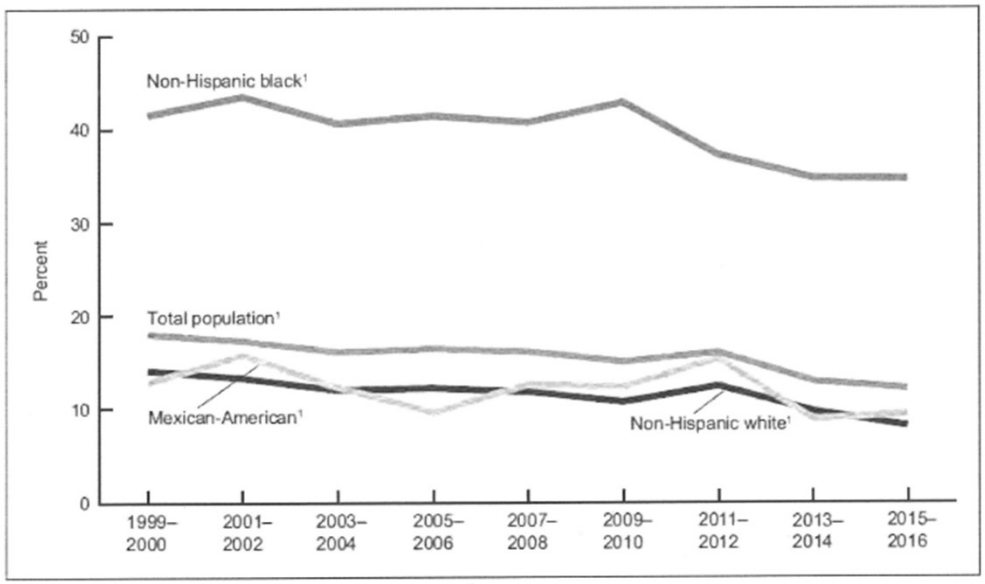

Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# HSV-2 seroprevalence has decreased over time, overall and in all racial/ethnic groups




[1] Significant decreasing linear trend over time, p<0.05

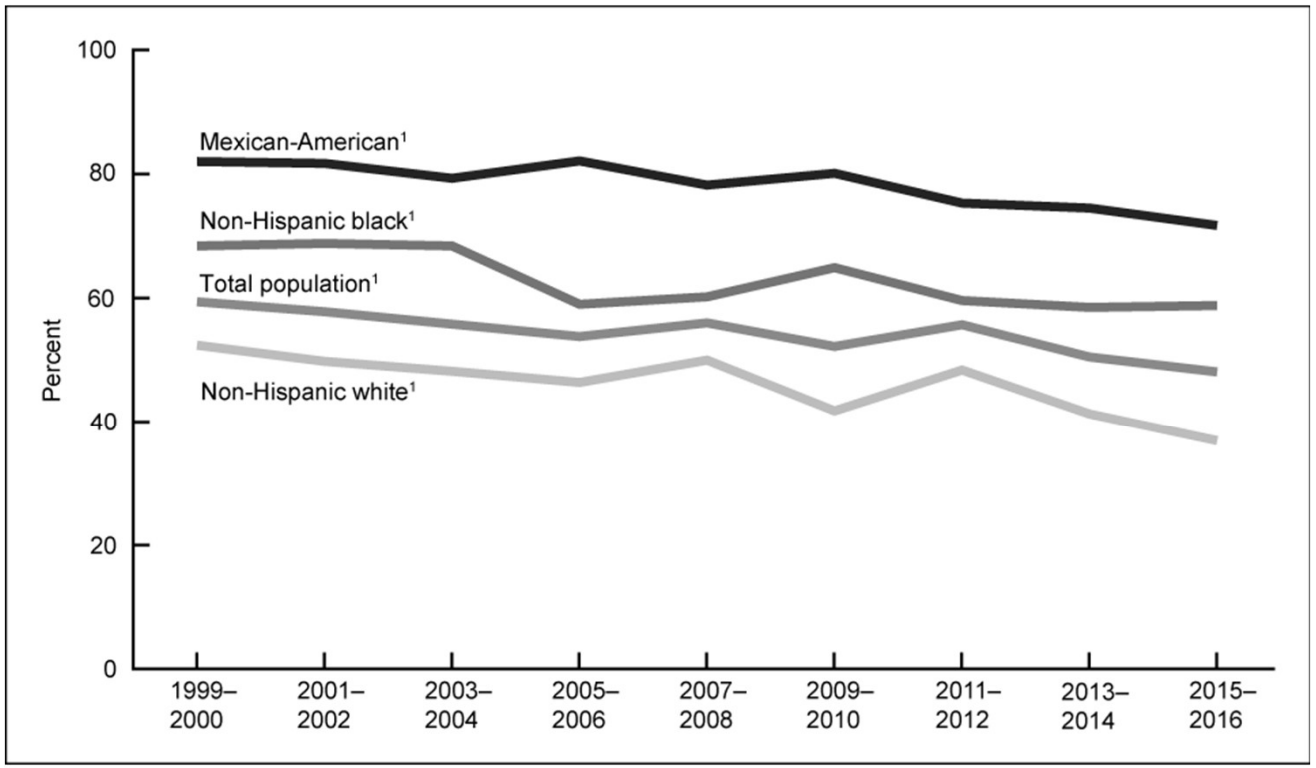
NOTES: Age adjusted by the direct method to the 2000 US Census population, using age groups 14-19, 20-29, 30-39, and 40-49 years. Total population includes all race and Hispanic origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population.

McQuillan, et al. NCHS Data Brief 2018.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

Figure 2. Trends in age-adjusted prevalence of herpes simplex virus type 1 among persons aged 14–49, for the total population and by race and Hispanic origin: United States, 1999–2000 through 2015–2016



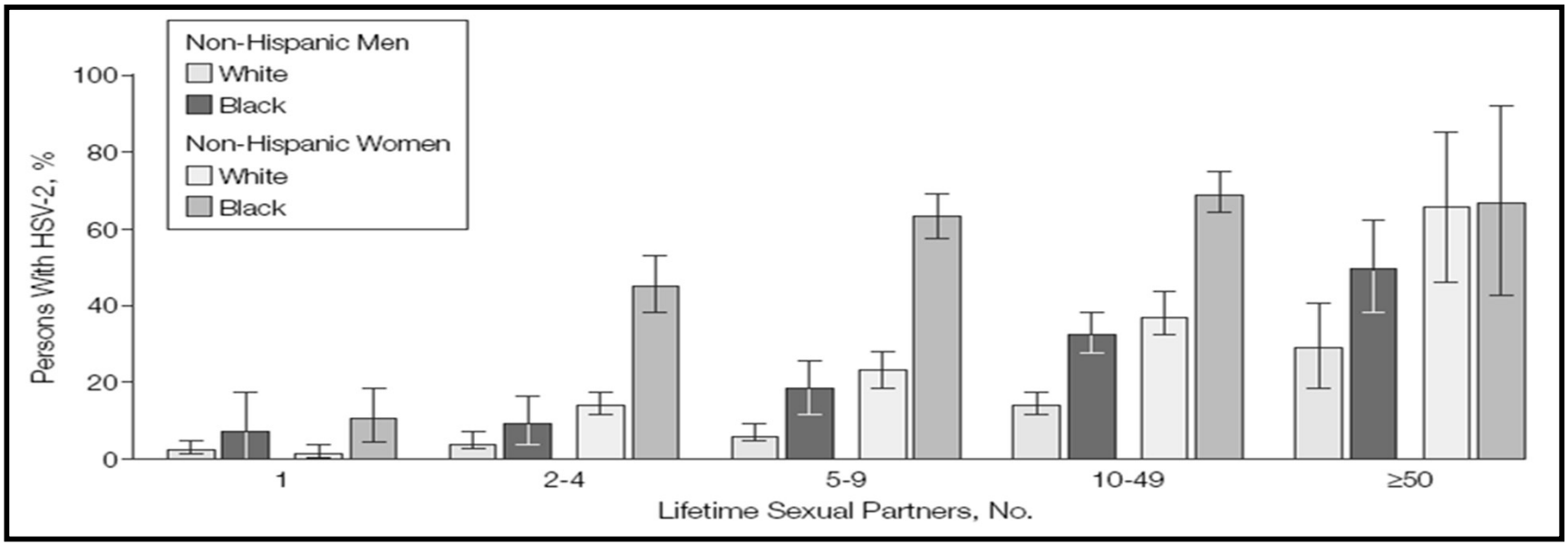

[1]Significant decreasing linear trend over time, $p < 0.05$.
NOTES: Age adjusted by the direct method to the 2000 U.S. Census population, using age groups 14–19, 20–29, 30–39, and 40–49 years. Total population includes all race and Hispanic-origin groups including those not shown separately. Data for the Asian subpopulation are only available since 2011, so this subpopulation is not shown separately, but included in the total population. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db304_table.pdf#2.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Age-Adjusted Herpes Simplex Virus Type 2 Seroprevalence

## According to the Lifetime Number of Sex Partners by Race/Ethnicity and Sex on NHANES in 1999-2004

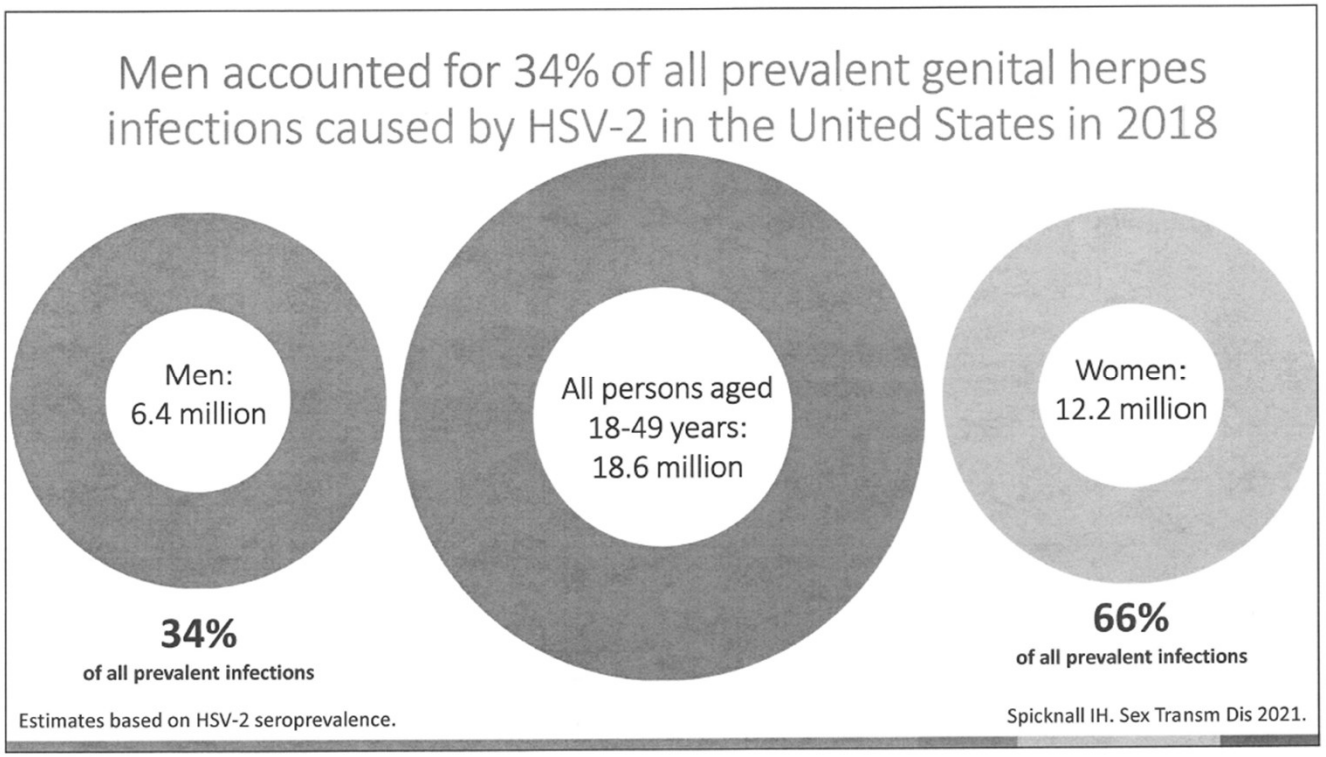



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

JAMA, August 23/30, 2006 Vol 296 No 8 pg 967



© 2026 Infectious Disease Board Review

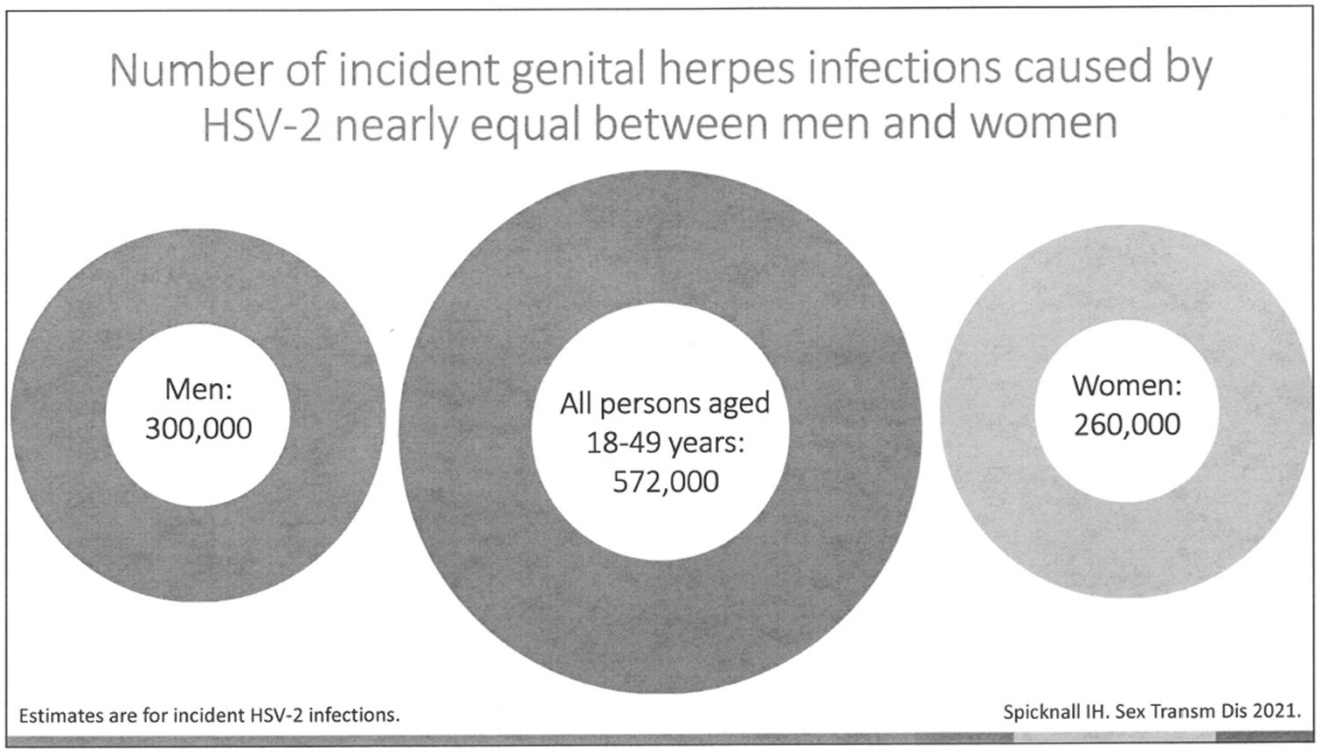



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**43 Herpes Simplex and Varicella Zoster**

*Speaker: Richard Whitley, MD*

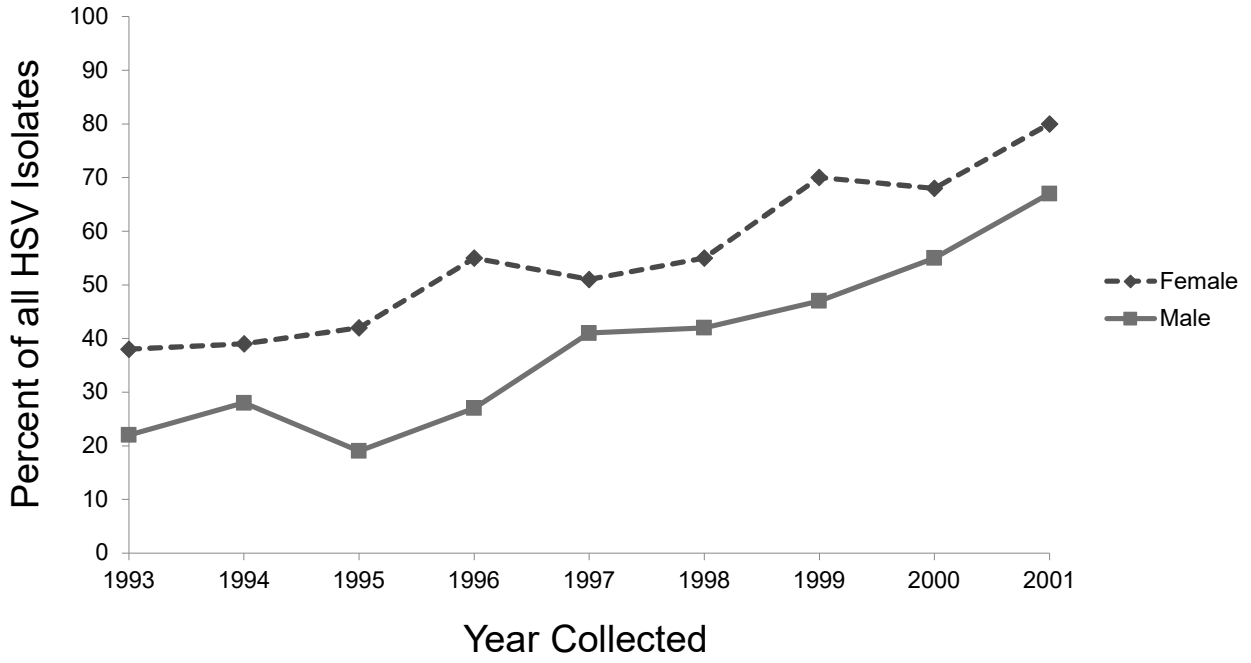
© 2026 Infectious Disease Board Review




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# HSV-1 Genital Isolates Among U.S. College Students




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

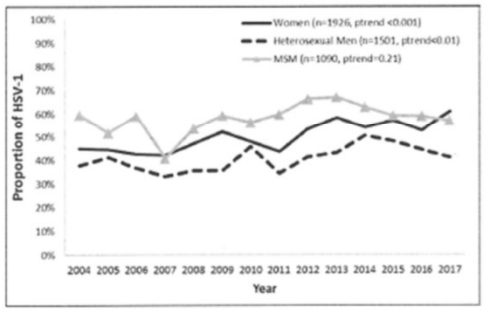
Sex Transm Dis 2003;30:797-800



© 2026 Infectious Disease Board Review

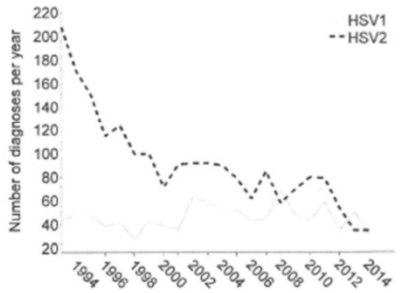
# Changing epidemiology of first episode genital herpes

**Melbourne Sexual Health Center**




In 2017, 54% of first episode genital herpes was due to HSV-1

**Public Health-Seattle & King County**



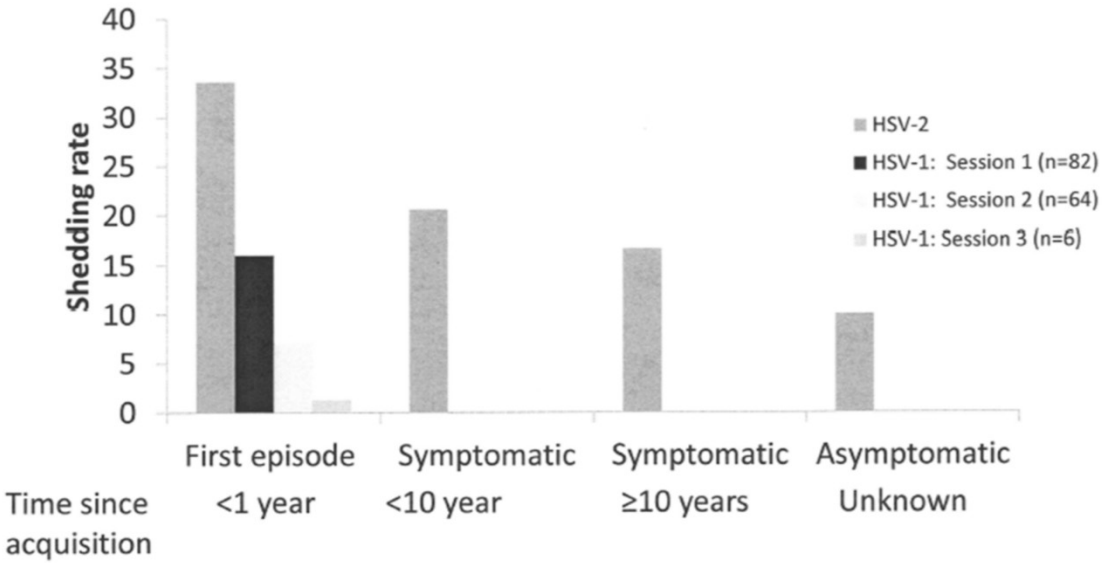

Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Genital Shedding Rate: HSV-2 vs. HSV-1

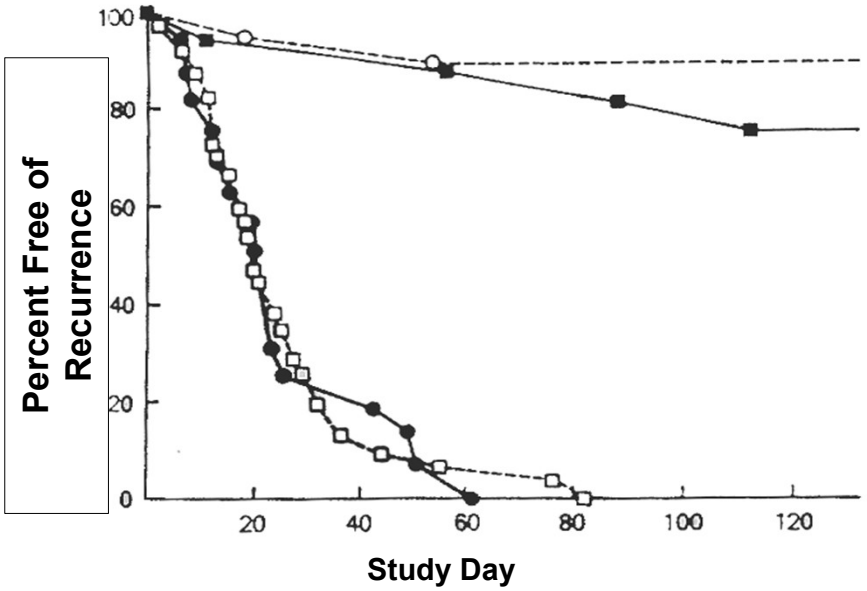



Johnston et al, ISSTDR 2019
Phipps *et al*, JID 2011
Tronstein *et al*, JAMA 2011

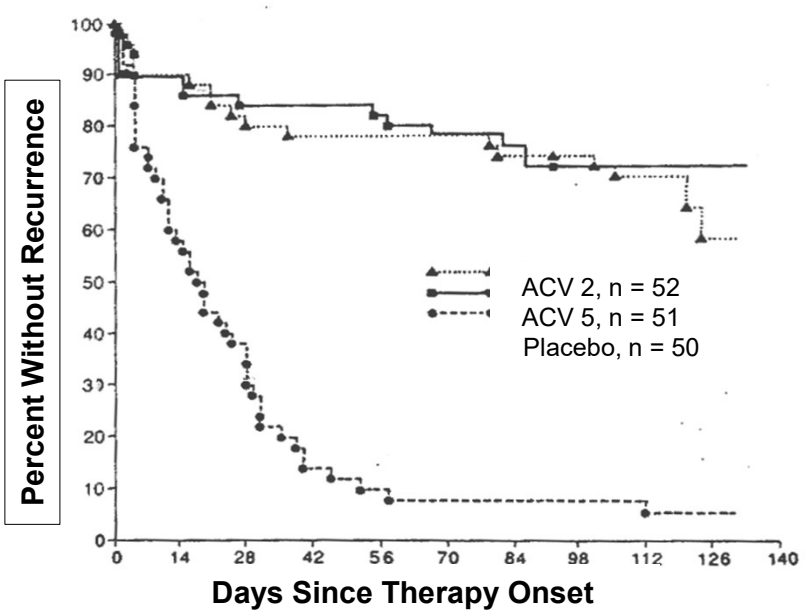
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes




Straus, et al. *NEJM*, 1984



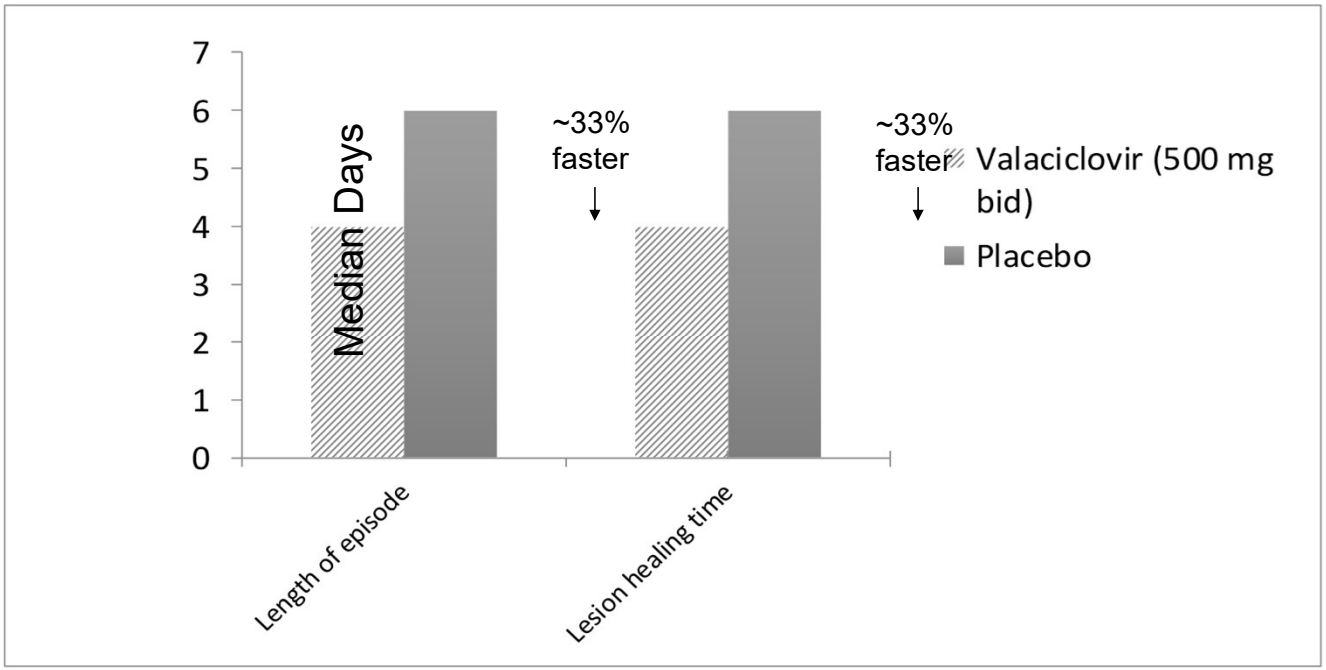

Douglas, et al, *NEJM*, 1984

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

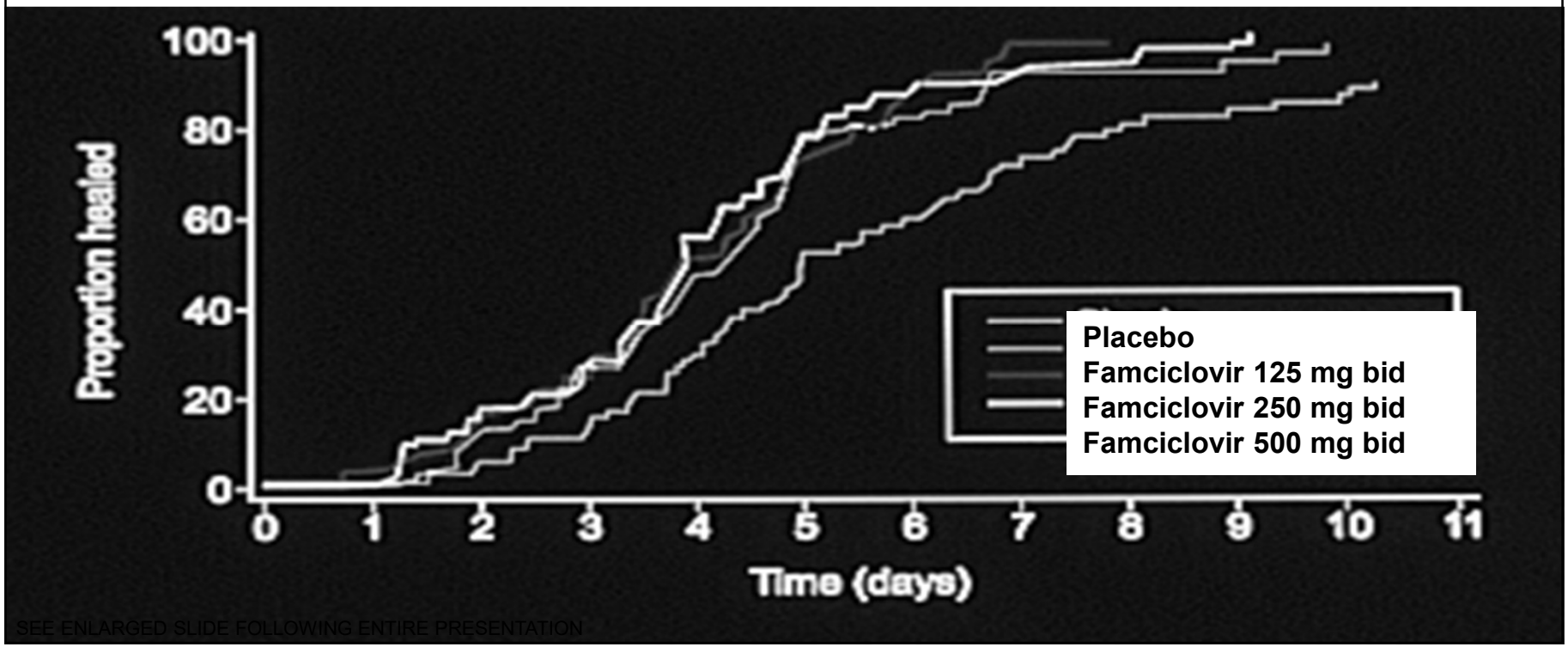
# Therapy of Recurrent Genital Herpes
## Duration of Disease




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


© 2026 Infectious Disease Board Review

# Famciclovir Therapy of Recurrent Genital Herpes

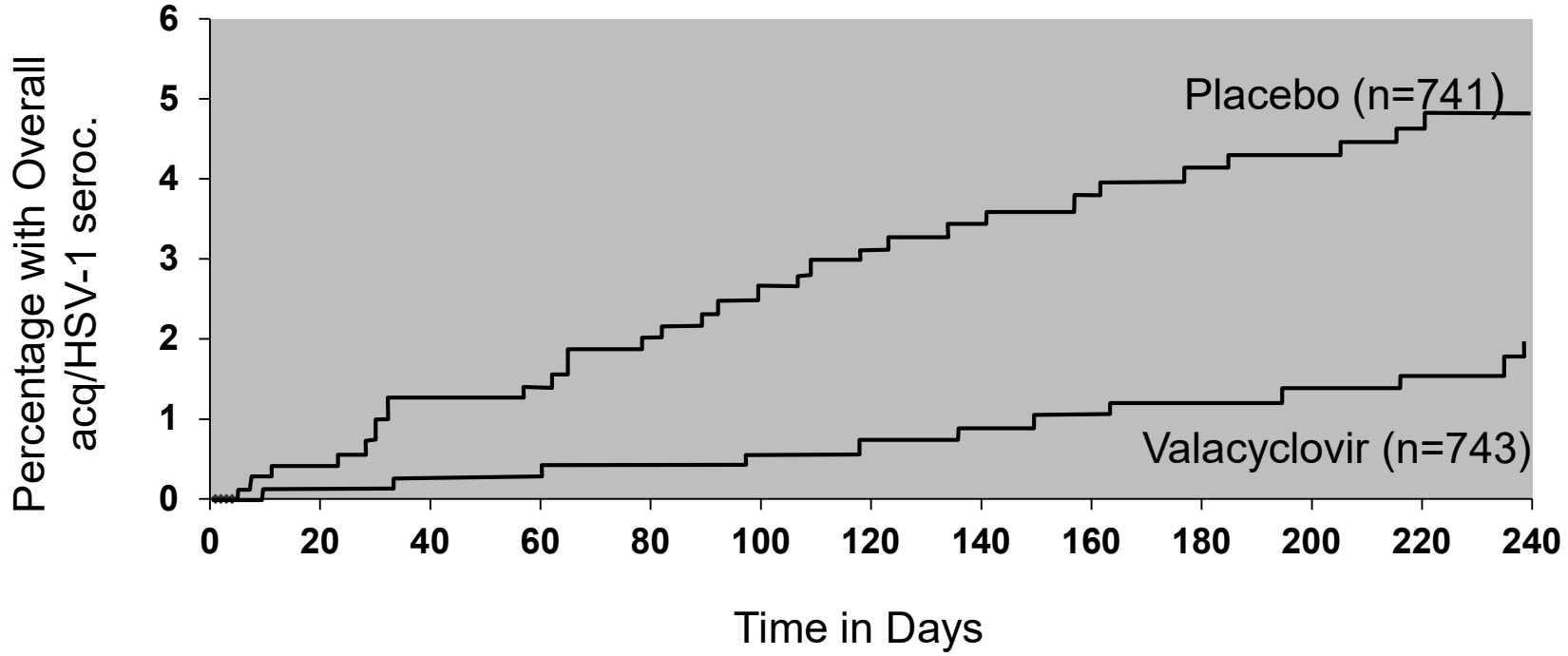



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners

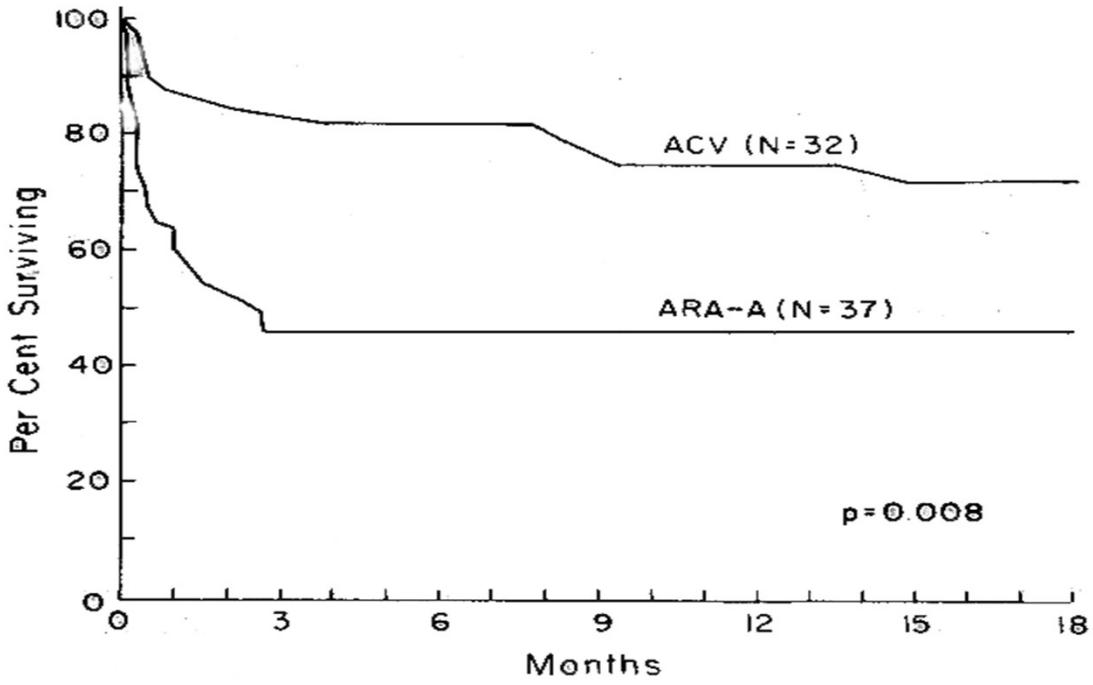



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Herpes Simplex Encephalitis Survival




**Vidarabine (ARA-A)**

**Vs.**

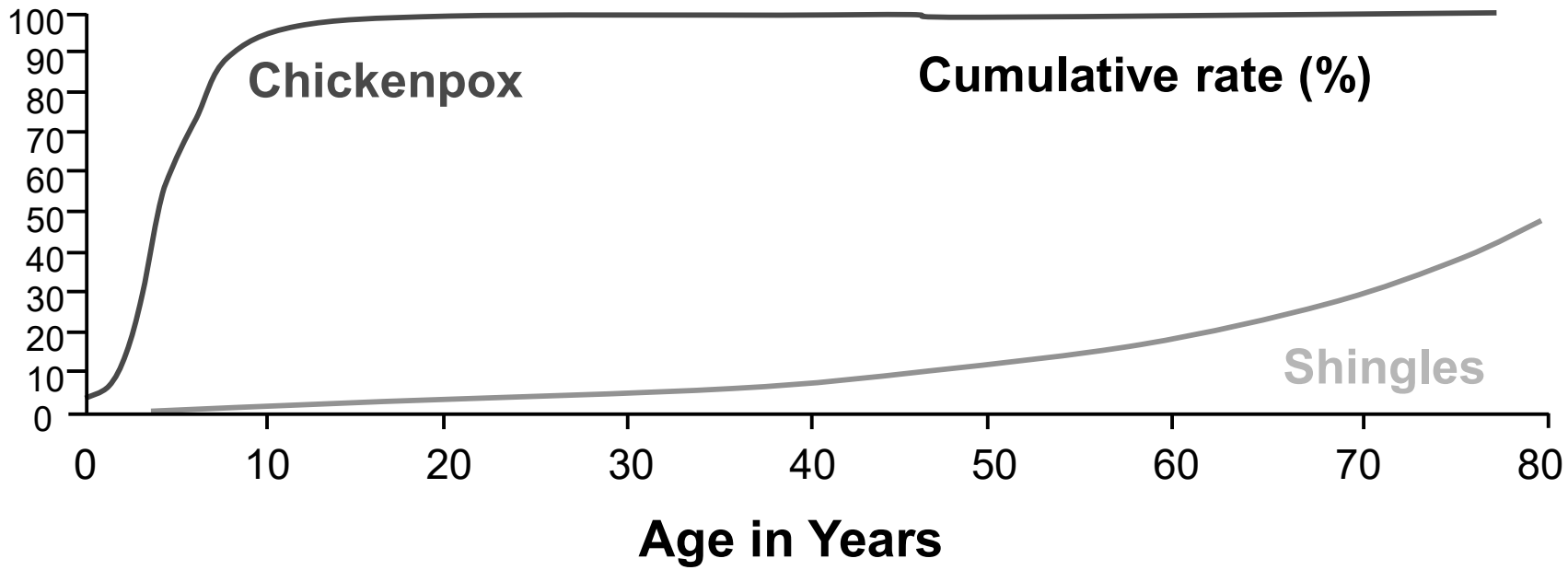
**Acyclovir (ACV);**
**P=0.008**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Varicella Zoster Virus Infection



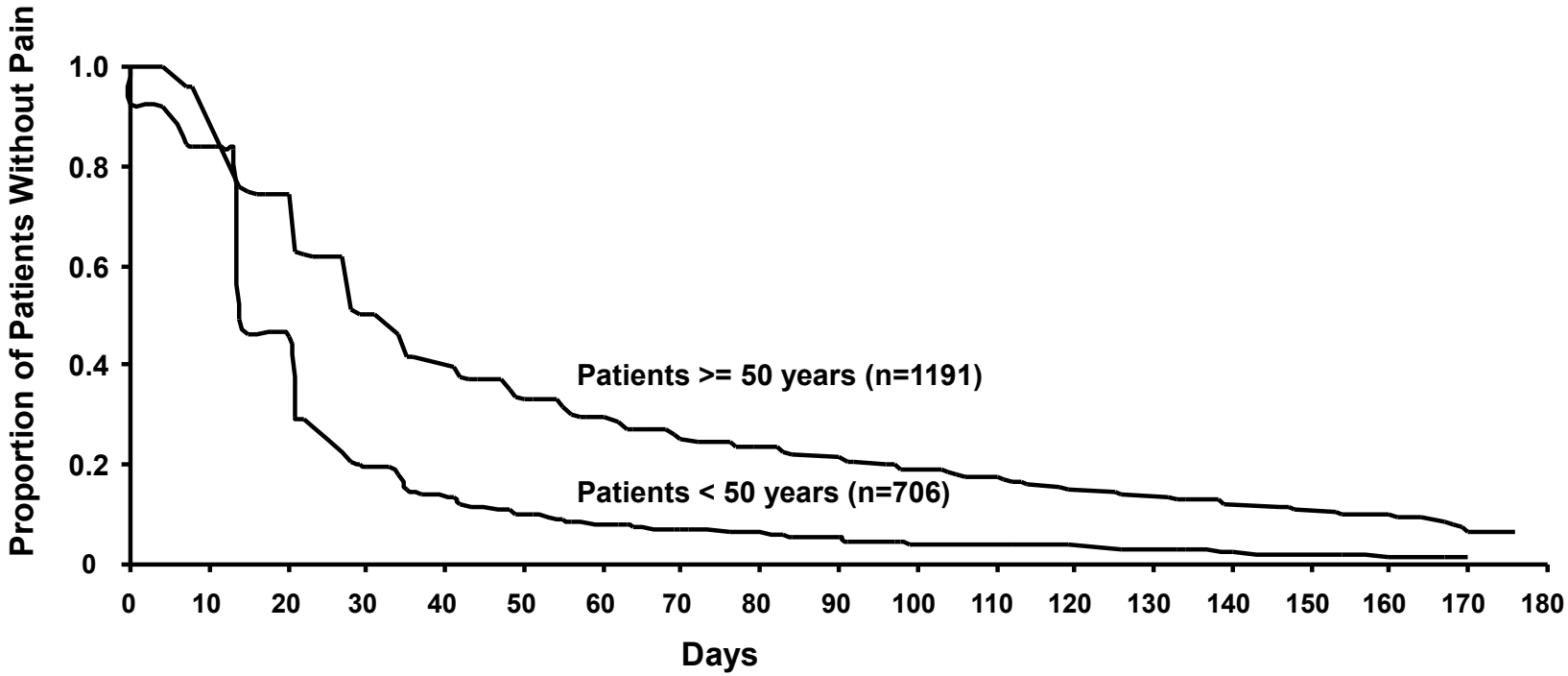

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368



© 2026 Infectious Disease Board Review

# Time to Cessation of Zoster Associated Pain

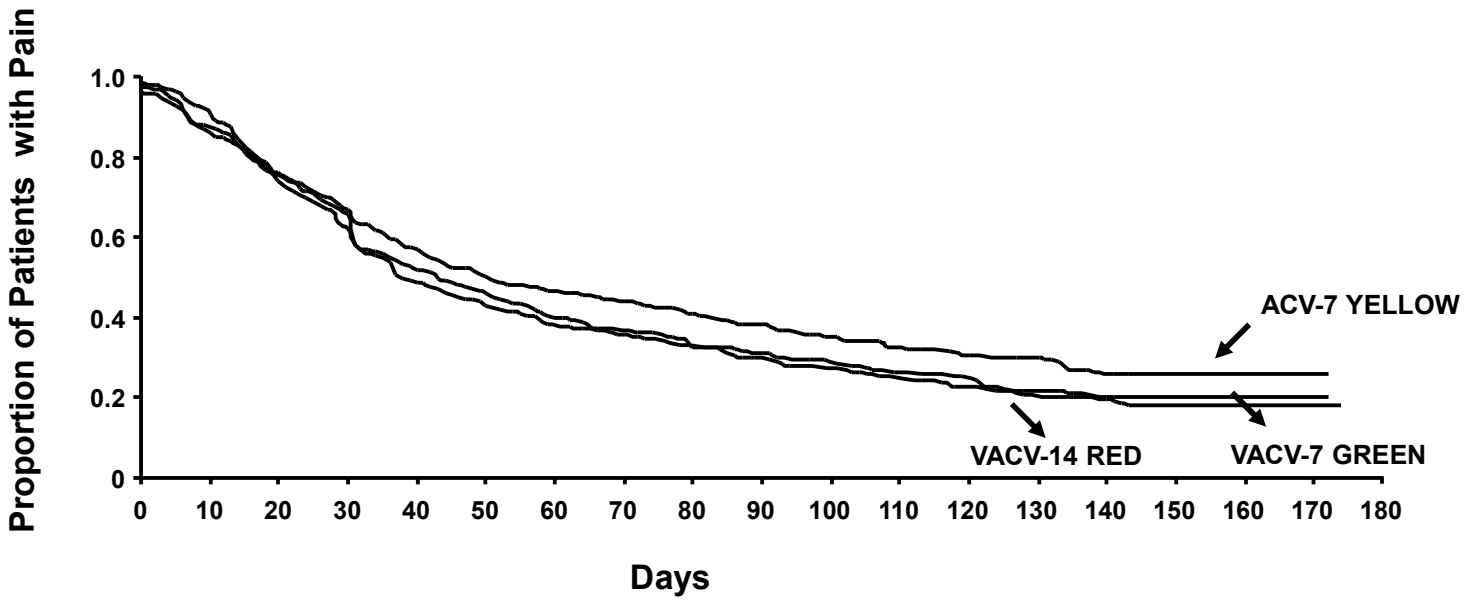



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

# Time to Cessation of Zoster Associated Pain n=1141



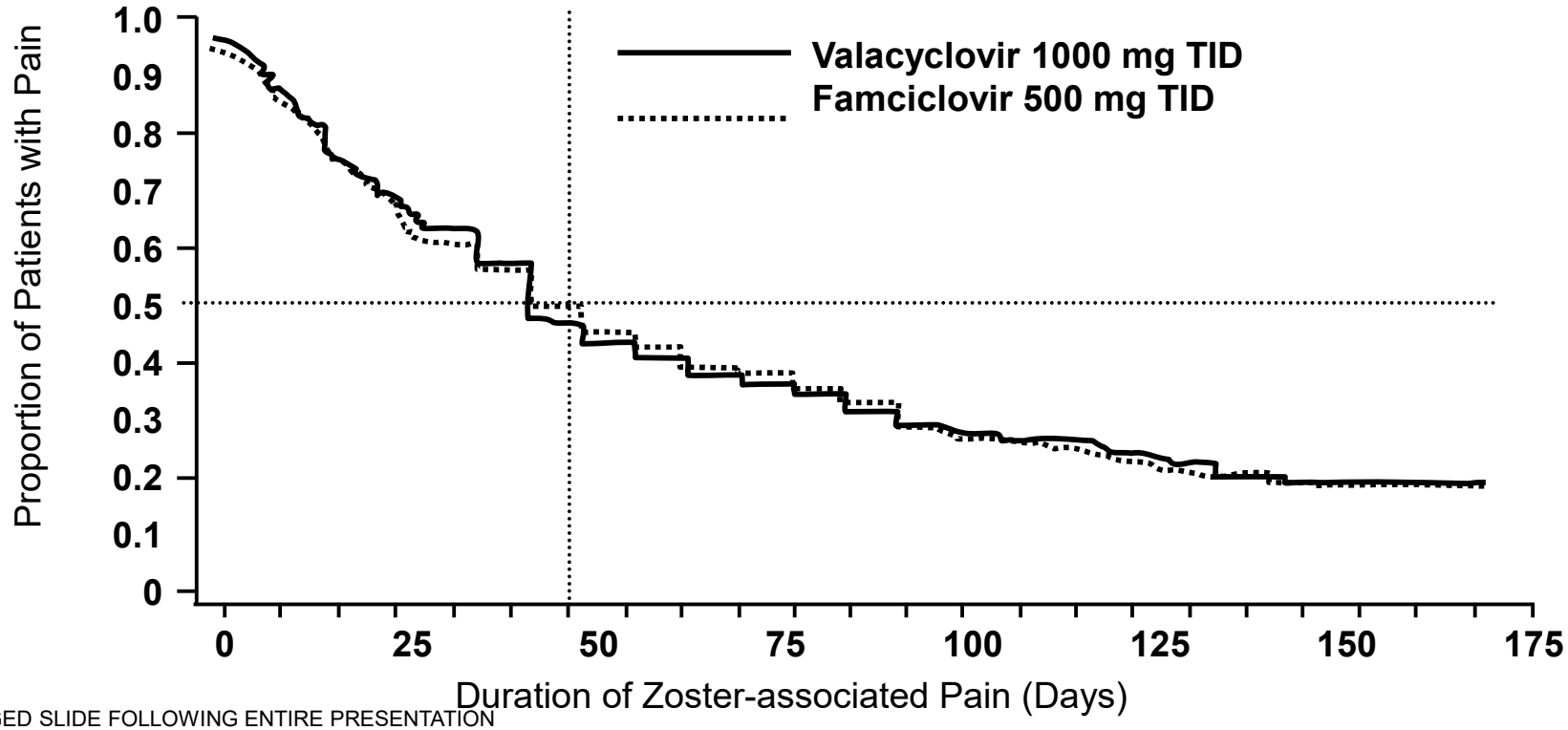

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.



© 2026 Infectious Disease Board Review

# Resolution of Pain in Herpes Zoster with Valacyclovir and Famciclovir




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



© 2026 Infectious Disease Board Review

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

Rajesh Gandhi, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




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

**Rajesh T. Gandhi, MD**

**Massachusetts General Hospital**
**Professor of Medicine, Harvard Medical School**
**Boston, Massachusetts**

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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

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

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

## Question #1

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

**Epidemiologic History**

- Patient was single and not sexually active.
- Hiked in New Hampshire. Denied known tick bites. Dog; no other animal exposures.

**Physical Examination**

- Appeared well. T 103.5, BP 104/50, HR 122, RR 18
- No rash or adenopathy. Remainder of exam normal.



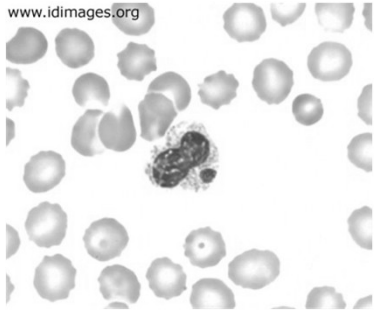
© 2026 Infectious Disease Board Review

## Question #1

**Studies**

- WBC 2.3 (51% P, 29% bands, 14% L, 4% atypical lymphocytes)
- Hct 39%
- Platelets 24.
- Chemistries, including liver enzymes, normal.
- Blood cultures negative.
- CXR: normal

Neutrophil with additional finding



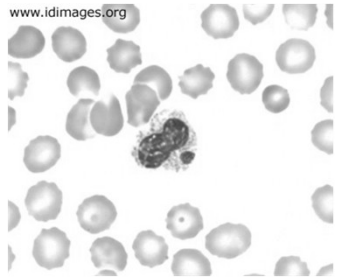

Contributed by Anne Kasmar, M.D.

## Question #1

**What is the diagnosis?**

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

Neutrophil with additional finding



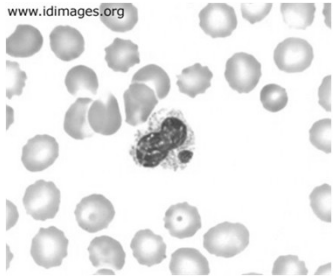

Contributed by Anne Kasmar, M.D.

## Question #1

**What is the diagnosis?**

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

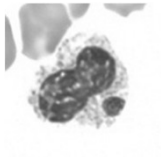
Neutrophil with additional finding




Contributed by Anne Kasmar, M.D.

## Diagnosis and Follow-up

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



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

**44 Photo Opportunity**

*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Anaplasmosis



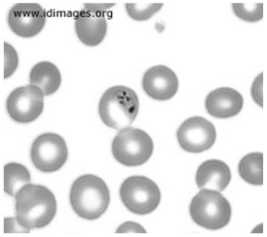
- New England, north central states and West Coast.
- *Anaplasma phagocytophilum* transmitted by tick *Ixodes scapularis*.
- Sx: fevers, chills, myalgias, headache. Rash <10%.
- Labs: leukopenia, thrombocytopenia, elevated transaminases.
- Dx: visualization of intraleukocytic bacteria (morulae) on blood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

## Rule out coinfection with Lyme, Babesia (same vector)

Lyme



Babesia




## Differential diagnosis

- **Meningococcemia:** no meningeal signs or rash to suggest acute meningococcemia; no arthritis/tenosynovitis/rash to suggest chronic meningococcemia
- **Histoplasmosis:** patient not immunosuppressed, which predisposes to disseminated histo; CXR not abnormal (infiltrates often present in histo)
- **Babesia:** ring-forms in red cells, not white cells
- **Rocky Mountain Spotted Fever:** would not explain morulae in neutrophils. RMSF (and human monocytotropic ehrlichiosis) more common in southeast, south central US

## Question #2

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

**Epidemiologic history**

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

**Contributed by Dr. Dave Patel**



© 2026 Infectious Disease Board Review

## Question #2

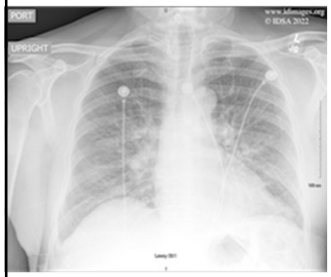
**Physical Examination**

- Mild respiratory distress
- BP 141/80. HR 94. 98 ºF, RR 20, $O_2$ 93% on 6 L oxygen (nasal canula)
- Respiratory exam: rhonchi at lung bases. Exam 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 negative
- *Legionella pneumophila* urine antigen were negative
- Respiratory viral panel negative

## Question #2




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



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

## Question #2

**Clinical Course Prior to Diagnosis**

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

## Question #2

### What is the diagnosis?



A. Coccidioidomycosis

B. Legionella pneumonia

C. Hantavirus Cardiopulmonary Syndrome

D. Leptospirosis Pulmonary Hemorrhage Syndrome

E. Tularemia



**44 Photo Opportunity**

*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Question #2

### What is the diagnosis?





A. Coccidioidomycosis

B. Legionella pneumonia

**C. Hantavirus Cardiopulmonary Syndrome**

D. Leptospirosis Pulmonary Hemorrhage Syndrome

E. Tularemia

## Follow-up

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

## Hantavirus Cardiopulmonary Syndrome (HCPS): Clues

- Most cases 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

## Question #3

- A man in his fifties presented with diarrhea, nausea, and vomiting of three days' duration
- Recently 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 US from Caribbean two decades ago; returned to visit one year ago
- **Physical Exam:** Temp 98.6. Mild epigastric tenderness. Remainder of exam normal



© 2026 Infectious Disease Board Review

## Question #3

**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. Klebsiella isolated from blood cultures (4/4 bottles) and cerebrospinal fluid

## Question #3

Abdominal CT:
colonic wall inflammation




**What is the diagnosis?**

A. Amebic infection
B. Strongyloides hyperinfection syndrome
C. Ascariasis
D. Fascioliasis
E. Colon cancer

## Question #3

Abdominal CT:
colonic wall inflammation




**What is the diagnosis?**

A. Amebic infection
**B. Strongyloides hyperinfection syndrome**
C. Ascariasis
D. Fascioliasis
E. Colon cancer

Gram stain of sputum




Iodine stain of stool




**44 Photo Opportunity**
*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Strongyloides Hyperinfection Syndrome

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

## Different Patient
## Larva currens: Cutaneous Strongyloidiasis

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



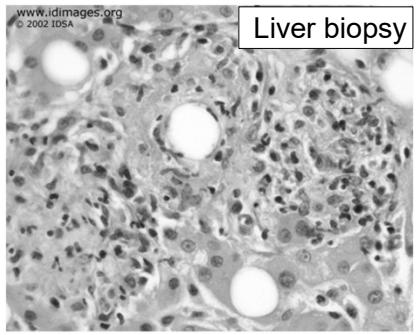

## Question #4

- Man in his 20s presented with nine days of vomiting, diarrhea, fever, headaches.
- Lived on farm with goats, chickens, guinea pigs, turkeys, cats, dogs.

- Exam: Appeared acutely ill. T104.4°F. Exam otherwise normal.
- Studies: AST 111, ALT 79, Alkaline Phosphatase 146

Contributed by Paul M. Jost, M.D,

## Question #4




Liver biopsy

**What is the diagnosis?**

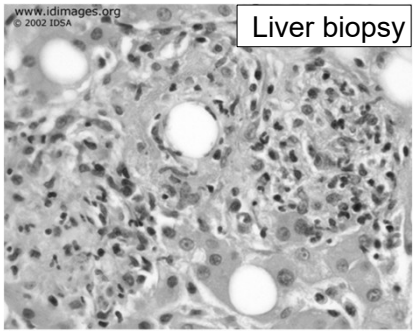
A.Coxiella
B.Cryptococcus
C.Histoplasma
D.Cyclospora
E.Bartonella

Contributed by Paul M. Jost, M.D,

**44 Photo Opportunity**
*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Question #4




Liver biopsy

**What is the diagnosis?**

**A.Coxiella**
B.Cryptococcus
C.Histoplasma
D.Cyclospora
E.Bartonella

Contributed by Paul M. Jost, M.D,

## *Coxiella* and "doughnut" granulomas

- *Coxiella burnetii* (agent of Q fever): exposure to infected ruminants (parturient goats, cattle, sheep).
- Transmission usually occurs by inhalation.
- Acute disease: fever, pneumonia and/or hepatitis.
- "Doughnut" granuloma (dense fibrin ring, central lipid vacuole) characteristic of Q fever
  - May also be seen in Hodgkin's disease, EBV and Cytomegalovirus infections, drug hypersensitivity

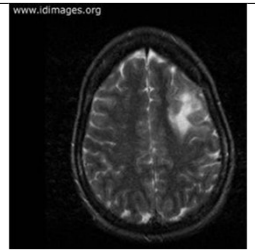
## Question #5

- 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.

Contributed by Wendy Yeh, M.D.

## Question #5

- **Physical exam:** 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)




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

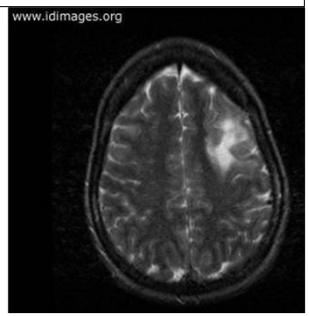
**44 Photo Opportunity**
*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Question #5

**What is the most likely diagnosis?**

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

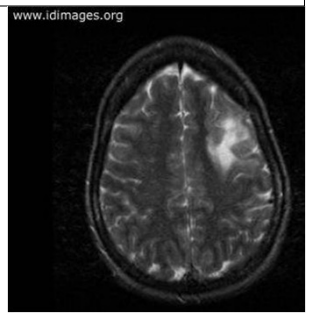



MRI: Abnormal T2 signal involving white matter, left fronto-parietal region. No enhancement, edema, mass effect

## Question #5

**What is the most likely diagnosis?**

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

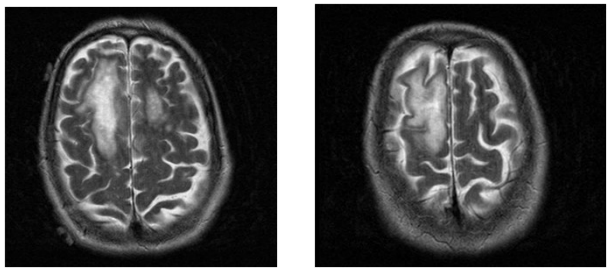



MRI: Abnormal T2 signal involving white matter, left fronto-parietal region. No enhancement, edema, mass effect

## 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, rituximab)
- Rapidly progressive focal neurologic deficits, usually due to cerebral white matter disease
- Rx: reversal of immunodeficiency. In people with HIV: antiretroviral therapy

## PML



**Contributed by Vince Marconi, M.D.**



© 2026 Infectious Disease Board Review

## 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.

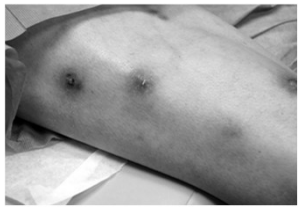
## Question #6

- 63 yo M with history of renal transplant developed multiple erythematous, raised, pruritic lesions on his thighs over the course of several weeks.
- **Past medical history:** ESRD due to post-streptococcal glomerulonephritis, s/p cadaveric renal transplant ; HCV infection.
- **Meds:** prednisone 15 mg qd; azathioprine 150 mg qd
- **Social history:** Healthy cat at home. Lived in rural Maryland near farm animals and frequently saw deer in his yard. Avid gardener but recalled no recent puncture wounds. Several tick bites in past year.
- **Travel history:** Mexico 2 yrs ago.

Contributed by Raj Gandhi, M.D.

## Question #6

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





## Question #6

**Studies**

- WBC 3.3; Hematocrit 26%; Platelets 118,000
- BUN 59 mg/dL, Creatinine 2.1 mg/dL
- AST 70; Alkaline Phosphatase 321.
- CXR: normal
- Blood Cultures: no growth

Contributed by Raj Gandhi, M.D.


© 2026 Infectious Disease Board Review

## Question #6

### What is the diagnosis?

A. Cryoglobulinemic vasculitis related to HCV infection
B. Nocardiosis
C. Nontuberculous mycobacteria
D. Cutaneous aspergillus
E. Botryomycosis




Contributed by Raj Gandhi, M.D.

## Question #6

### What is the diagnosis?

A. Cryoglobulinemic vasculitis related to HCV infection
B. Nocardiosis
**C. Nontuberculous mycobacteria**
D. Cutaneous aspergillus
E. Botryomycosis




Contributed by Raj Gandhi, M.D.

## Diagnosis and Follow-up

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

## *M. chelonae*

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


© 2026 Infectious Disease Board Review

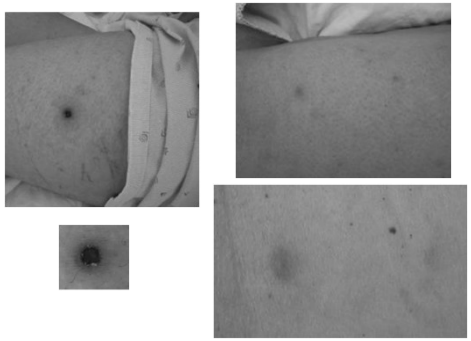
## Question #7

- 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. Denied sexual activity.
- **PE:** appeared well. T 100.5. No adenopathy. Lesion present on left thigh. Papular erythematous rash on extremities, back, chest.

## Question #7

**What does this patient most likely have?**

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

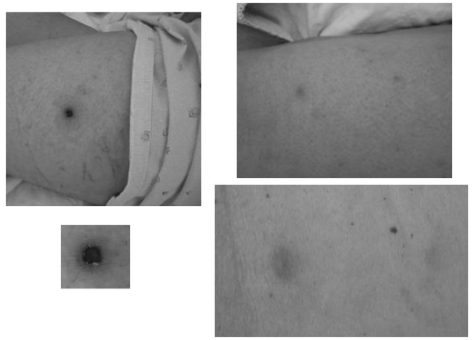


Case contributed by Karen Thomas, M.D. and Leena Gandhi, M.D., Ph.D

## Question #7

**What does this patient most likely have?**

A. Varicella
B. Mpox
C. Cutaneous anthrax
**D. Rickettsialpox**
E. Lyme



## Rickettsialpox

- *Rickettsia akari*, member of spotted fever group of rickettsiae
- Transmitted to humans by mouse mite
- NYC outbreak in 1980s; high seroprevalence (16%) in people who inject drugs 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



© 2026 Infectious Disease Board Review

## 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 |

**Rickettsialpox** **Chickenpox**








## Question #8

- 55 yo M was admitted with nephrolithiasis and *E. coli* urosepsis.
  - Course was complicated by ARDS, requiring prolonged ventilatory support and a tracheostomy.
  - On hospital day 21, he developed a nosocomial MRSA pneumonia.
  - On hospital day 28, he developed new fever and rash.
- **Past medical history:** Hypertension. Atrial fibrillation
- Medications: vancomycin, nifedipine, digoxin, coumadin.

Contributor: John Beigel, M.D.

## Question #8

- **Exam:** T 103.2. Erythematous areas in axillae, back, thigh. Bullae with yellow, serous, non-purulent fluid
- WBC 15.7 (84% P, 9% L, 3% M, 3% E). Bullous fluid cultures negative




**44 Photo Opportunity**

*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Question #8

**What does this patient most likely have?**

A. Dermatitis herpetiformis
B. Bullous pemphigoid
C. Linear IgA bullous disease from vancomycin
D. Herpes zoster
E. Staphylococcal scalded skin syndrome



Contributor: John Beigel, M.D.

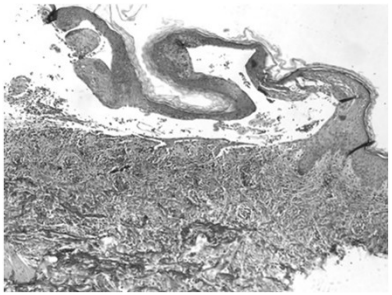
## Question #8

**What does this patient most likely have?**

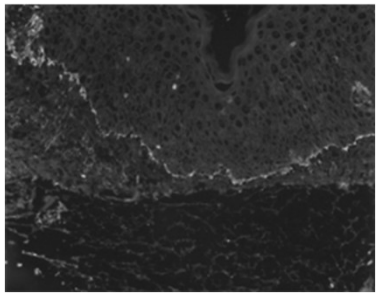
A. Dermatitis herpetiformis
B. Bullous pemphigoid
**C. Linear IgA bullous disease from vancomycin**
D. Herpes zoster
E. Staphylococcal scalded skin syndrome



Contributor: John Beigel, M.D.



H & E: neutrophilic infiltrate at dermal-epidermal junction; sub-epidermal bulla



Immunofluorescence: IgA deposition, basement membrane, dermal-epidermal junction

## Treatment/Follow Up

Vancomycin was discontinued, and the bullae gradually resolved after one week.



**44 Photo Opportunity**
*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Linear IgA Bullous Disease

- Rare autoimmune subepidermal blistering disorder; usually idiopathic.
- Vesiculobullous eruption of the skin and MM
- Linear IgA deposition along the basement membrane zone
- Drug-induced LABD is most often due to iv vancomycin use.
- Generally resolves with discontinuation of vancomycin. May recur with rechallenge.

57

## Question #9

- 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.

Contributors: Drs. Isaac Bogoch, Rajesh Gandhi

## Question #9

**Physical exam**

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





## Question #9

**Labs:**

- 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



**44 Photo Opportunity**

*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

## Question #9

**What is the diagnosis?**

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





## Question #9

**What is the diagnosis?**

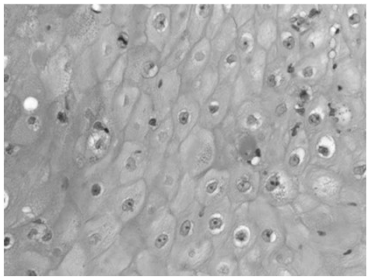
A. Botryomycosis due to *S. aureus*
B. Nocardia
C. Brucella
**D. Orf**
E. Salmonella





## 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

## 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)



© 2026 Infectious Disease Board Review

## 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

## 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



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

**44 Photo Opportunity**
*Speaker: Rajesh Gandhi, MD*

© 2026 Infectious Disease Board Review

**Wednesday, August 26, 2026**

---

**45**

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

**Henry Chambers, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Endocarditis of Native and Prosthetic Valves, Infections of Cardiac Implantable Devices

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

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- Merck – Stock and DSMB member
- Moderna - Stock

## Topics for Discussion

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

## Diagnosis of Endocarditis



©2026 Infectious Disease Board Review, LLC

## 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

## Question #1

### Which one of the following statements is correct?

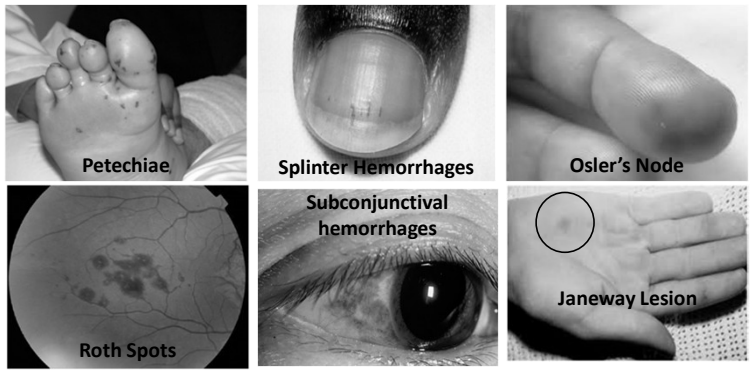
1. **Staphylococcus aureus is the most common cause of bacterial endocarditis***
2. Dental procedures carry a substantial risk for streptococcal endocarditis for patients with predisposing cardiac lesions
3. Three-quarters of patients with endocarditis have a known underlying cardiac predisposing condition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

## 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

## Microvascular/Immunologic Phenomena





©2026 Infectious Disease Board Review, LLC

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

*Clinical Infectious Diseases*
VIEWPOINTS

# The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria

Vance G. Fowler, Jr.,[1,2,©] David T. Durack,[1] Christine Selton-Suty,[3] Eugene Athan,[4] Arnold S. Bayer,[5,6] Anna Lisa Chamis,[1] Anders Dahl,[7] Louis DiBernardo,[1] Emanuele Durante-Mangoni,[8] Xavier Duval,[9] Claudio Querido Fortes,[10] Emil Fosbøl,[11] Margaret M. Hannan,[12] Barbara Hasse,[13] Bruno Hoen,[14] Adolf W. Karchmer,[15] Carlos A. Mestres,[16] Cathy A. Petti,[1,17] Maria Nazarena Pizzi,[18] Stephen D. Preston,[19] Albert Roque,[20] Francois Vandenesch,[21,22] Jan T. M. van der Meer,[23] Thomas W. van der Vaart,[23] and Jose M. Miro[24,25]

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

## 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<br><br>OR<br><br>Vegetation, leaflet destruction, or adjacent cardiac tissue showing inflammatory changes | Two major criteria<br><br>OR<br><br>Five minor criteria<br><br>OR<br><br>One major plus three minor criteria | Three minor criteria<br><br>OR<br><br>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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 2023 Duke-ISCVID Major Criteria

| Positive Blood Cultures | Imaging | Surgical |
|---|---|---|
| Typical microorganisms* from 2 separate blood cultures<br>OR<br>Non-typical organisms in 3 or more separate blood cultures<br>OR<br>+ 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<br>1) Vegetation, leaflet perforation, aneurysm, abscess, pseudo-aneurysm, fistula OR<br>2) New regurgitation c/w prior imaging OR<br>3) NEW PVE dehiscence<br><br>+ PET/CT<br>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

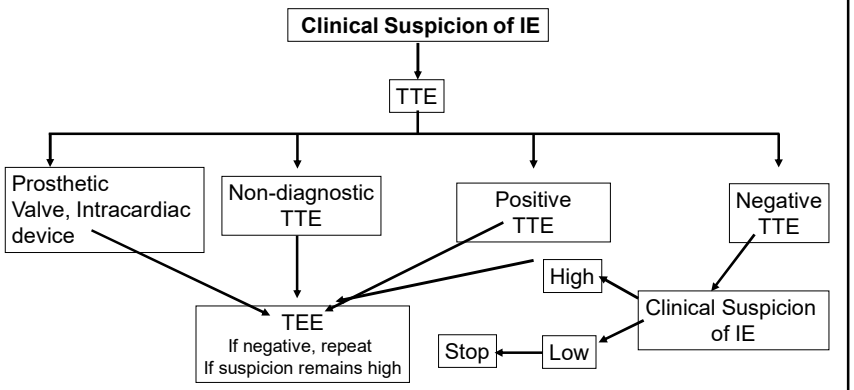
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Role of Echocardiography




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

European Heart Journal (2015) 36, 3075–3123

## 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 >38.0ºC (>100.4ºF)
- 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

## Possible Endocardits Rates with Duke Criteria

| | 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

## Native Valve Endocarditis

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Question #2

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

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

## Question #2

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

A. Nafcillin
B. Vancomycin
C. Vancomycin + nafcillin
D. Vancomycin + gentamicin
E. Vancomycin + gentamicin + rifampin

## Question #2

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

A. Nafcillin
**B. Vancomycin***
C. Vancomycin + nafcillin
D. Vancomycin + gentamicin
E. Vancomycin + gentamicin + rifampin

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## 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$^{o}$C
  - 3/6 holosystolic murmur, radiating 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 $\mu$g/ml, ceftriaxone MIC = 0.25 $\mu$g/ml

## Question #3

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

A. Penicillin for 6 weeks
B. Penicillin + gentamicin for 4 weeks
C. Ceftriaxone for 4 weeks
D. Penicillin + gentamicin for 2 weeks then penicillin for 2 weeks
E. Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

## Question #3

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

A. Penicillin for 6 weeks
B. Penicillin + gentamicin for 4 weeks
**C. Ceftriaxone for 4 weeks***
D. Penicillin + gentamicin for 2 weeks then penicillin for 2 weeks
E. Ceftriaxone + gentamicin for 2 weeks then ceftriaxone for 2 weeks

## Treatment of VGS 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)


©2026 Infectious Disease Board Review, LLC

## Question #4

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

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

## Question #4

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

A. Ampicillin for 2 weeks
B. Penicillin + gentamicin for 4 weeks
C. Ampicillin + gentamicin for 4 weeks
D. Ampicillin + ceftriaxone for 6 weeks
E. Daptomycin for 8 weeks

## Question #4

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

A. Ampicillin for 2 weeks
B. Penicillin + gentamicin for 4 weeks
C. Ampicillin + gentamicin for 4 weeks
**D. Ampicillin + ceftriaxone for 6 weeks***
E. Daptomycin for 8 weeks

## 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 $\geq$ 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

## HACEK Organisms

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

## Antimicrobial Therapy of HACEK Endocarditis

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

## Empirical Therapy for Endocarditis While Awaiting Culture Results

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

## Oral Therapy of Endocarditis


©2026 Infectious Disease Board Review, LLC

## 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

## Outcomes: POET Trial of Oral Therapy

1954 assessed for eligibility

↓

1554 excluded (428 no Duke criteria)

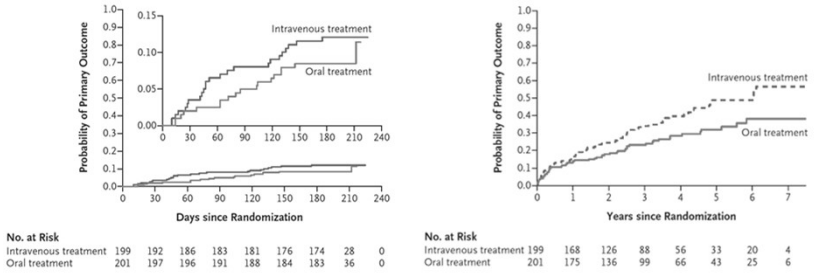
↓

400 randomized

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

N Engl J Med 2019;380:415

## Outcomes: POET Trial of Oral Therapy




N Engl J Med 2019;380:415




N Engl J Med 2019;380:1373

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Culture-Negative Endocarditis

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Question #5

**A 37-year-old marginally housed man 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

## Question #5

**What is the most likely diagnosis in this patient not feeling well for several weeks?**

A. Granulomatosis with polyangitis
B. Culture-negative endocarditis due to Staphylococcus aureus
C. Culture-negative endocarditis due to a viridans group streptococcal species
D. Culture-negative endocarditis due to Bartonella hensalae
E. Culture-negative endocarditis due to Tropheryma whipplei

## Question #5

**What is the most likely diagnosis in this patient not feeling well for several weeks?**

A. Granulomatosis with polyangitis
B. Culture-negative endocarditis due to Staphylococcus aureus
C. Culture-negative endocarditis due to a viridans group streptococcal species
**D. Culture-negative endocarditis due to Bartonella hensalae***
E. Culture-negative endocarditis due to Tropheryma whipplei

## 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


©2026 Infectious Disease Board Review, LLC

## 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:** Doxycycline 12 weeks plus rifampin first 6 weeks (or gent for the first 2 weeks)
- **Tropheryma whipplei:** Indolent, protracted course with arthralgias, diarrhea, malabsorption, weight loss, CNS involvement

## Tools for Diagnosis of Culture-Negative Endocarditis

| Organism | Clinical clues | Serology | Specific PCR | Universal 16s/18s rRNA PCR, 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Metagenomic Next Generation Sequencing

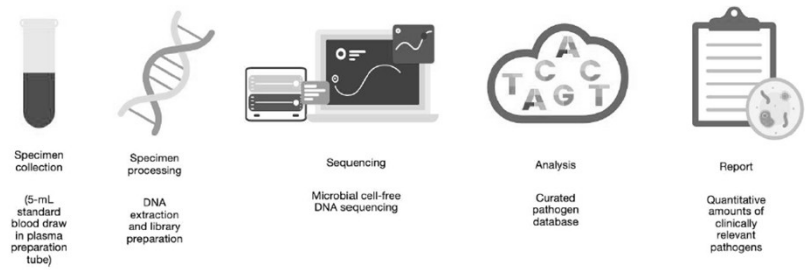



**Figure 1.** Microbial cell-free DNA testing process.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Clin Infect Dis. 2025 Jul 4:ciaf361. PMID 40614175.

## mNGS for Culture-negative Endocarditis

- Utility greatest when conventional microbiological studies are negative
- Unbiased, can detect rare non-cultivatable pathogens
- Information provided: microorganism, DNA quantitation (molecules/100 nanoliter), resistance gene detection
- Concordant with blood cultures (provided the pathogen is in the database), remains positive up to a month or longer
- Clinical impact, good or bad, not well characterized; criteria lacking

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## mNGS for Culture-negative Endocarditis
### -Mayo Experience-

| Diagnostic Categories | | Endocarditis (66) | No Endocarditis (70) |
|---|---|---|---|
| Endocarditis | Definite | 43 | 0 |
| | Possible | 23 | 41 |
| | Rejected | 0 | 29 |
| mNGS+ | CMT- | 22 (33%) | 20 (29%) |
| | CMT+ | 18 (27%) | 0 |
| mNGS- | CMT- | 18 (27%) | 50 (71%) |
| | CMT+ | 8 (12%) | 0 |

Open Forum Infect Dis. 2025; 2:ofaf099. PMID 40046887

# Prosthetic Valve and Device-Related Endocarditis

## Question #6

**A 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 100.2o F, Pulse 85 , BP 130/70mm Hg, RR 16

HEENT: oral cavity and tonsils red and swollen, no lymphadenopathy

Lungs: clear

Heart: No murmur

Skin: no rash

Rapid mgs strep, rapid flu both negative

## Question #6

**What is the best approach for managing this patient?**

A. Obtain throat culture and prescribe Pen VK while awaiting results
B. Obtain throat culture and give a script for Pen VK to be filled if culture is positive for GAS
C. Prescribe azithromycin for treatment of acute URI
D. Obtain blood cultures and await results
E. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin


©2026 Infectious Disease Board Review, LLC

## Question #6

**What is the best approach for managing this patient?**

A. Obtain throat culture and prescribe Pen VK while awaiting results
B. Obtain throat culture and give a script for Pen VK to be filled if culture is positive for GAS
C. Prescribe azithromycin for treatment of acute URI
**D. Obtain blood cultures and await results***
E. Obtain blood cultures and initiate therapy with vancomycin, gentamicin, and rifampin

## Diagnosis of PVE/TAVR

- 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

## 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

## Antimicrobial Therapy of PVE/TAVR

| 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 $\leq$ 0.12 $\mu$g/ml | Pen or ceftriaxone $\pm$ gent OR Vancomycin | 6 weeks (optional gent, 1$^{st}$ 2 wk)<br>6 weeks |
| Streptococci, MIC > 0.12 $\mu$g/ml | Pen or ceftriaxone + gent OR Vancomycin | 6 weeks<br>6 weeks |
| Enterococci | Same as for NVE | 6 weeks |


©2026 Infectious Disease Board Review, LLC

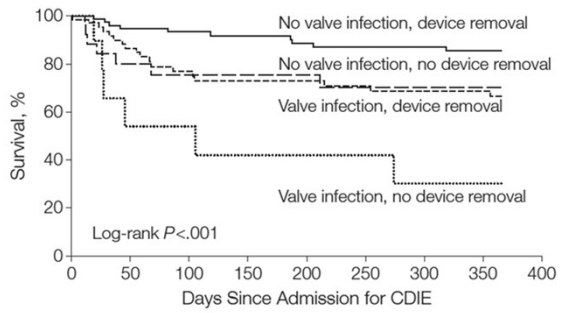
## Cardiac Implantable Device Infections
**(Permanent pacemakers, defibrillators)**

J Am Coll Cardiol 2008;49:1851; Circulation 2010;121:458; NEJM 2012;367:842; JAMA 2012;307:1727, Circulation 2024; 149:e201

## Cardiac Implantable Device Infection Types

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

## Survival with and without Device Removal




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Athan, JAMA. 2012; 307:1727-1735

## 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



©2026 Infectious Disease Board Review, LLC

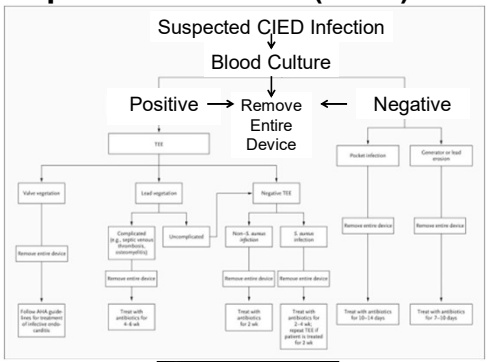
## Algorithm for Management of an Infected Cardiac Implantable Device (CIED) Infection



The NEW ENGLAND JOURNAL of MEDICINE

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

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

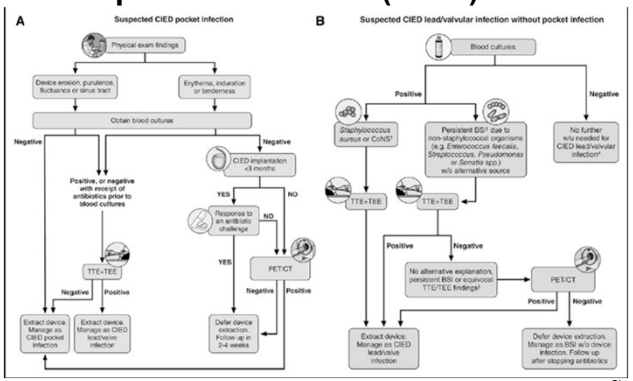



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

The NEW ENGLAND JOURNAL of MEDICINE

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

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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Circulation 2024; 149:e201

## 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 or PET/CT is negative
- No signs of pocket infection, suspected CIED infection + negative blood cultures or if positive not S. aureus or CoNS and clears in 72 hours or TTE/TEE negative + PET/CT negative

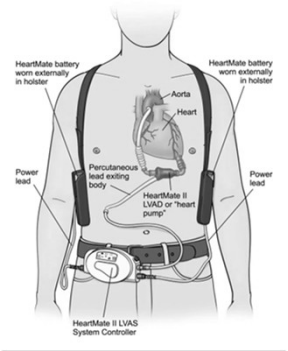
Circulation 2024; 149:e201

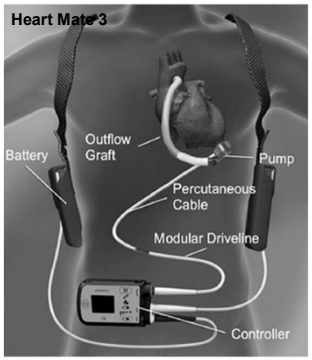
**45 Endocarditis of Native and Prosthetic Devices, and Infections of Pacers and Ventricular Assist Devices**

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Infection of Ventricular Assist Devices




## 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 Cardiothoracic Surg 2021;10:233; Clinical Transplantation 2019;33:e13552.

## Microbiology of VAD-Specific Infections

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

Clinical Transplantation 2019;33:e13552.

## Management and Therapy

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

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



©2026 Infectious Disease Board Review, LLC

## 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 Cardiothoracic Surg 2021;10(2):233-239

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Circulation. 2021;143:e963-e978

## Which Dental Procedures?

**YES**

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

**NO**

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

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## 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


©2026 Infectious Disease Board Review, LLC

# 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** |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



©2026 Infectious Disease Board Review, LLC

## 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<br><br>OR<br><br>Vegetation, leaflet destruction, or adjacent cardiac tissue showing inflammatory changes | Two major criteria<br><br>OR<br><br>Five minor criteria<br><br>OR<br><br>One major plus three minor criteria | Three minor criteria<br><br>OR<br><br>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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# 2023 Duke-ISCVID Major Criteria

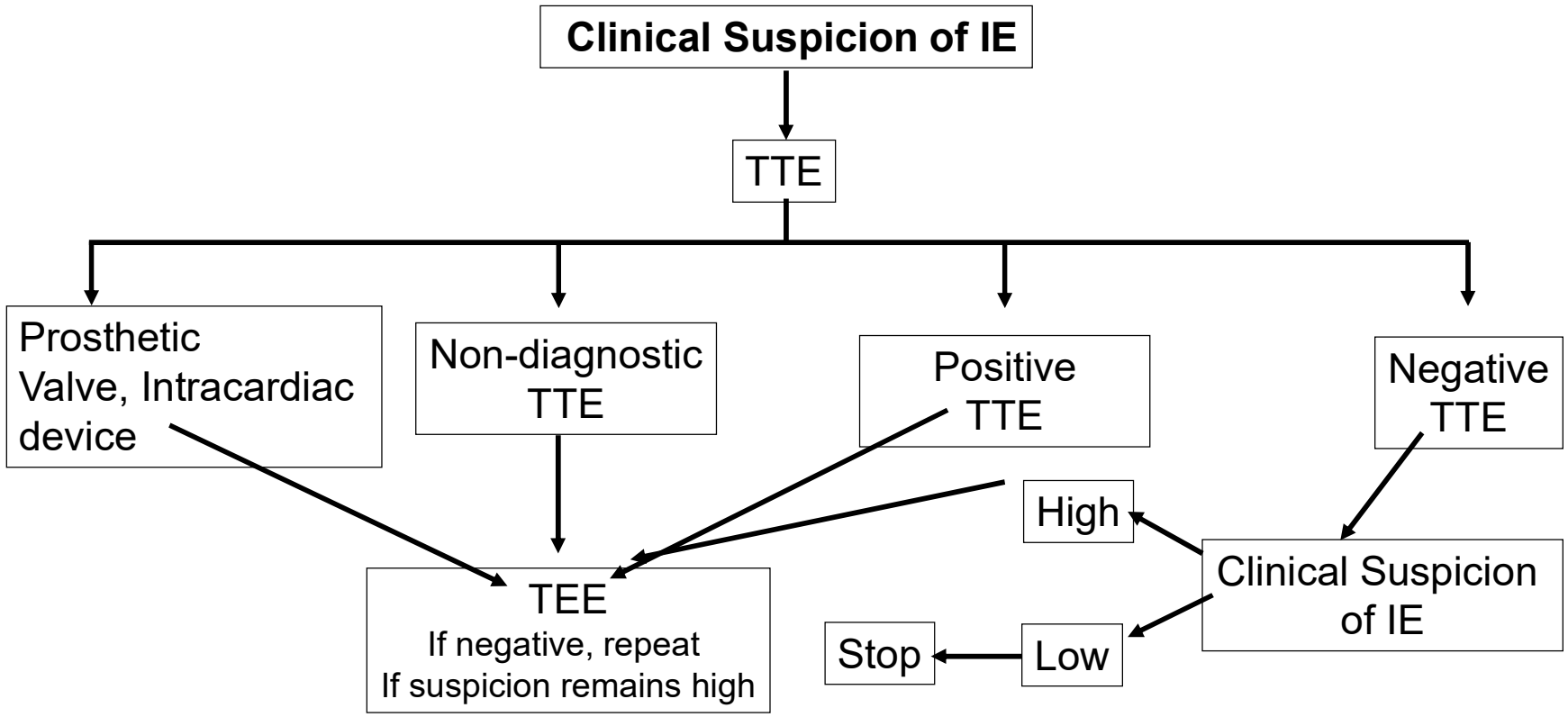
| Positive Blood Cultures | Imaging | Surgical |
|---|---|---|
| Typical microorganisms* from 2 separate blood cultures<br>OR<br>Non-typical organisms in 3 or more separate blood cultures<br>OR<br>+ PCR for Coxiella burnetti, Bartonella, T whipplei; Coxiella phase I IgG antibody titer >1:800, IFA IgG titer for Bartonella ≥ 1:800 | + ECHO/Cardiac CT<br>1) Vegetation, leaflet perforation, aneurysm, abscess, pseudo-aneurysm, fistula OR<br>2) New regurgitation c/w prior imaging OR<br>3) NEW PVE dehiscence<br><br>+ PET/CT<br>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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Role of Echocardiography




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

European Heart Journal (2015) 36, 3075–3123



©2026 Infectious Disease Board Review, LLC

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# 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 $\geq$ 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 |

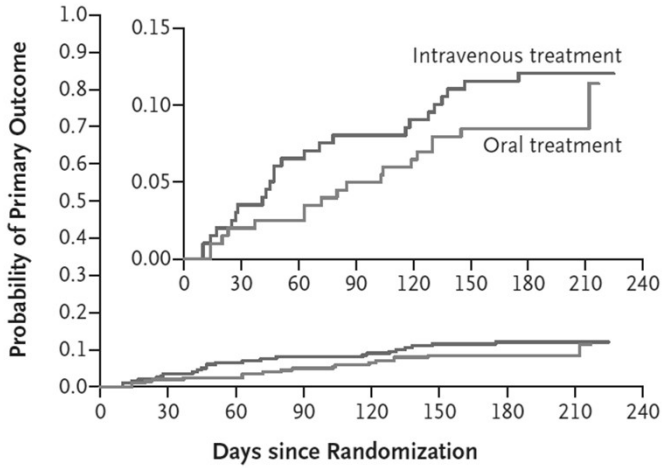
*Limited data that 2 weeks of gent is sufficient

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

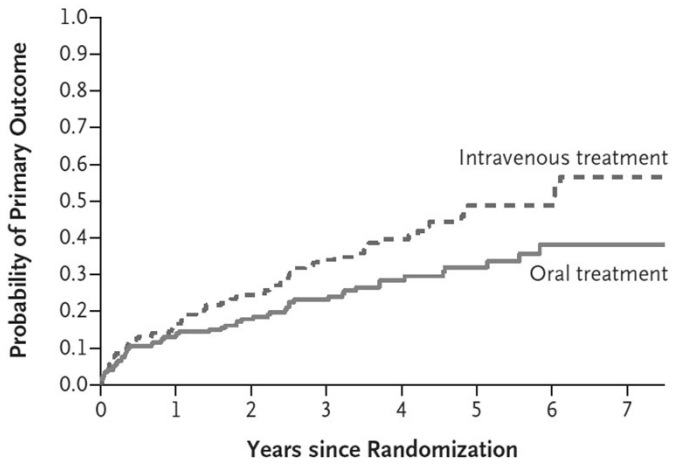
# Outcomes: POET Trial of Oral Therapy




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Intravenous treatment | 199 | 192 | 186 | 183 | 181 | 176 | 174 | 28 | 0 |
| Oral treatment | 201 | 197 | 196 | 191 | 188 | 184 | 183 | 36 | 0 |

N Engl J Med 2019;380:415




**No. at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Intravenous treatment | 199 | 168 | 126 | 88 | 56 | 33 | 20 | 4 |
| Oral treatment | 201 | 175 | 136 | 99 | 66 | 43 | 25 | 6 |

N Engl J Med 2019;380:1373

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Metagenomic Next Generation Sequencing

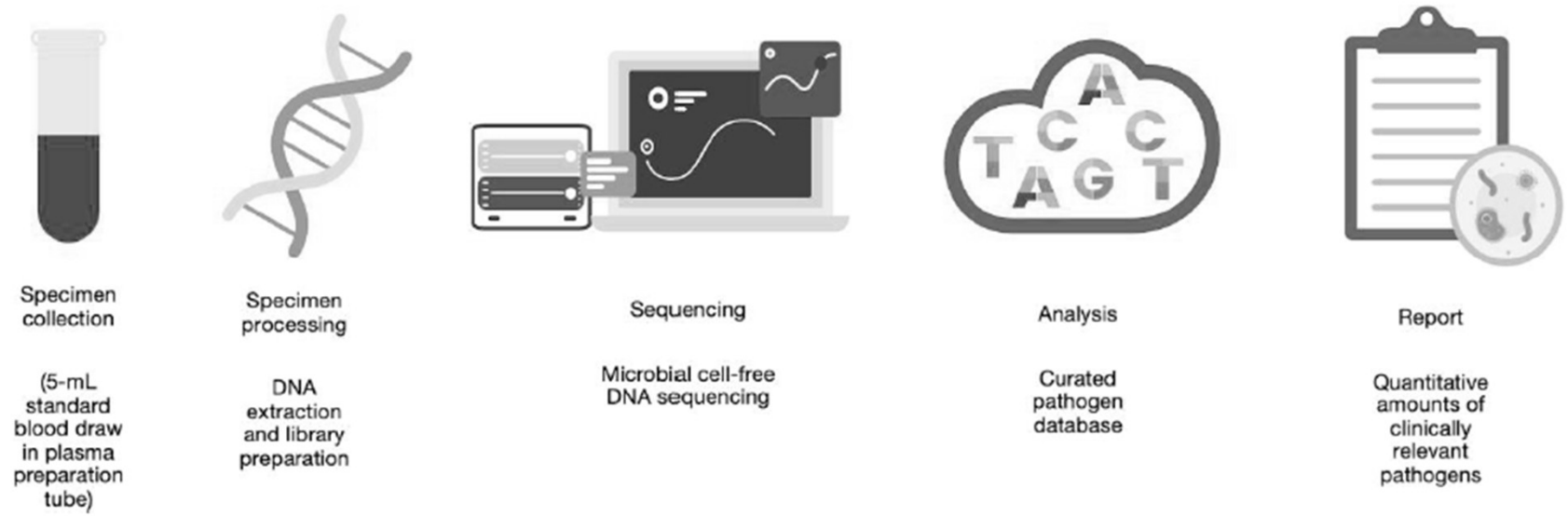



**Figure 1.** Microbial cell-free DNA testing process.

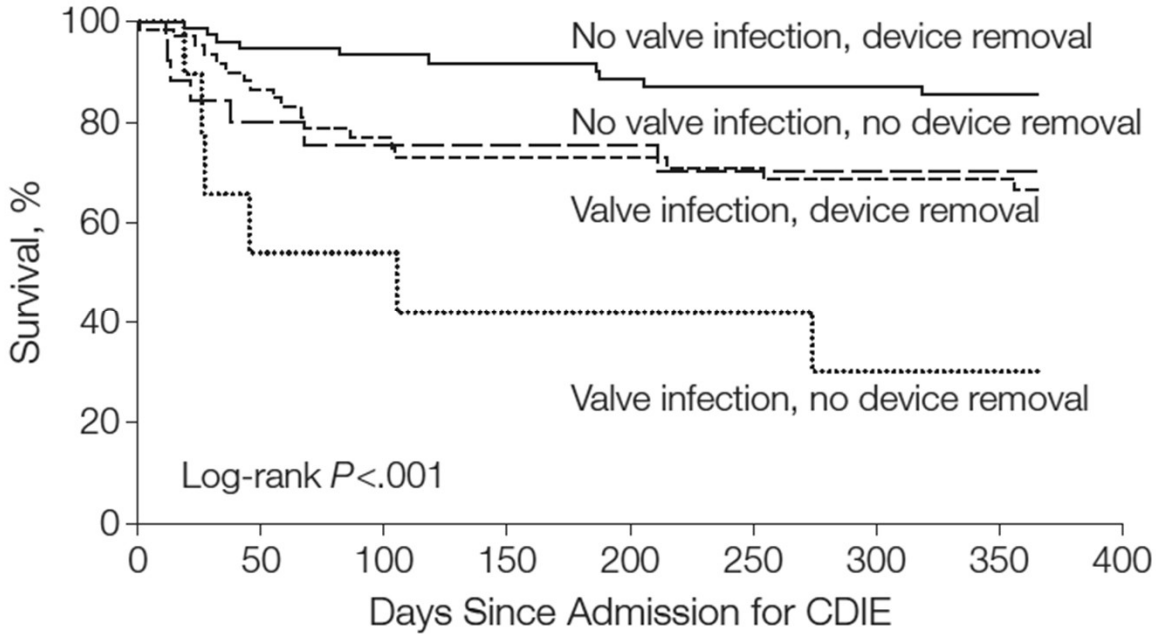
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Clin Infect Dis. 2025 Jul 4:ciaf361. PMID 40614175.



©2026 Infectious Disease Board Review, LLC

# Survival with and without Device Removal



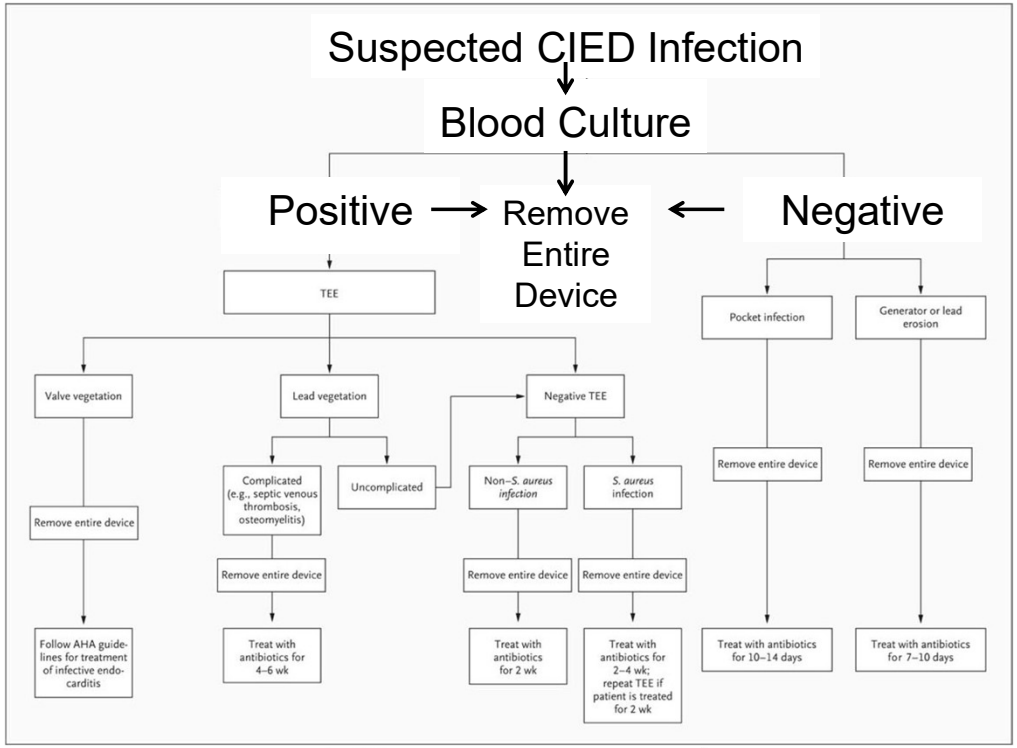

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Athan, JAMA. 2012; 307:1727-1735



©2026 Infectious Disease Board Review, LLC

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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

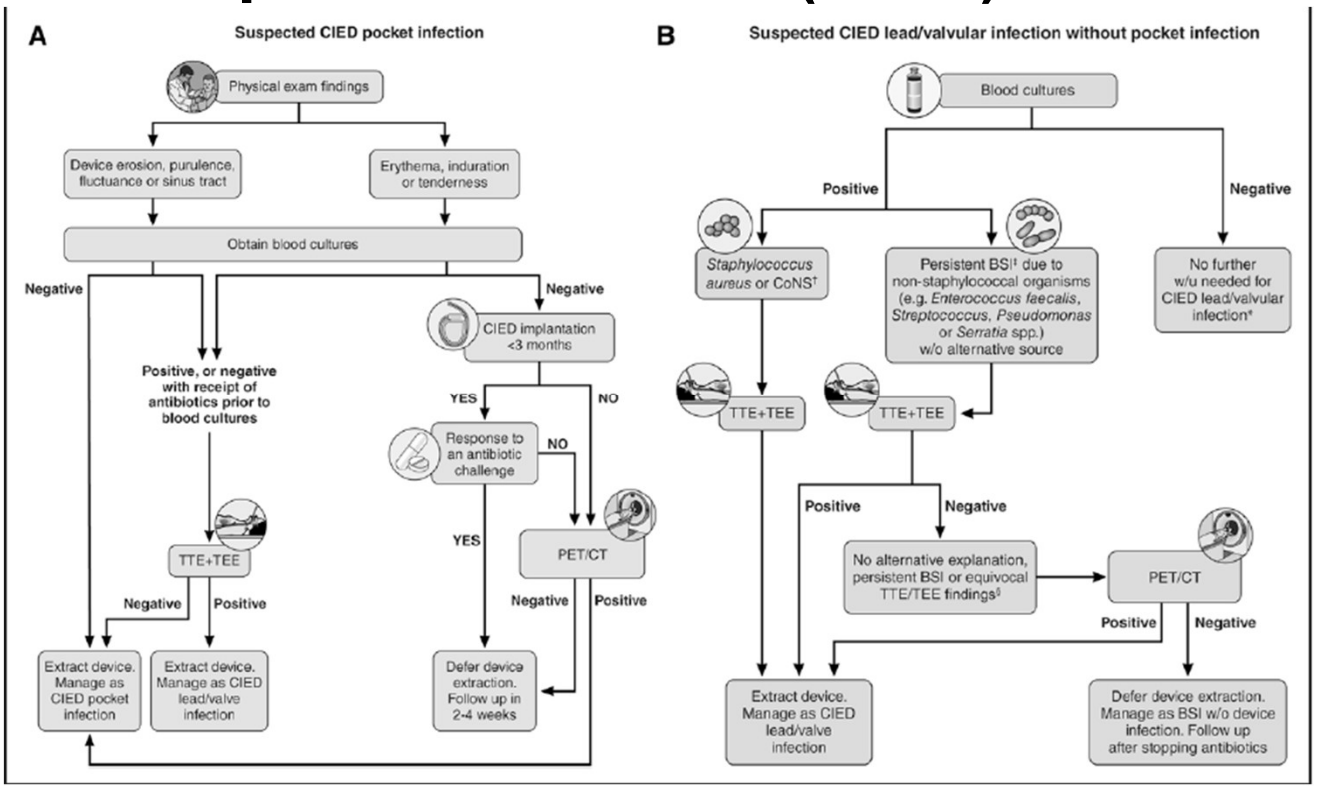
The NEW ENGLAND JOURNAL of MEDICINE

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



©2026 Infectious Disease Board Review, LLC

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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Circulation 2024; 149:e201

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

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

# 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 Cardiothoracic Surg 2021;10(2):233-239

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Circulation. 2021;143:e963-e978



©2026 Infectious Disease Board Review, LLC

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

Wednesday, August 26, 2026

46

# Acute Hepatitis

David Thomas, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Acute Hepatitis

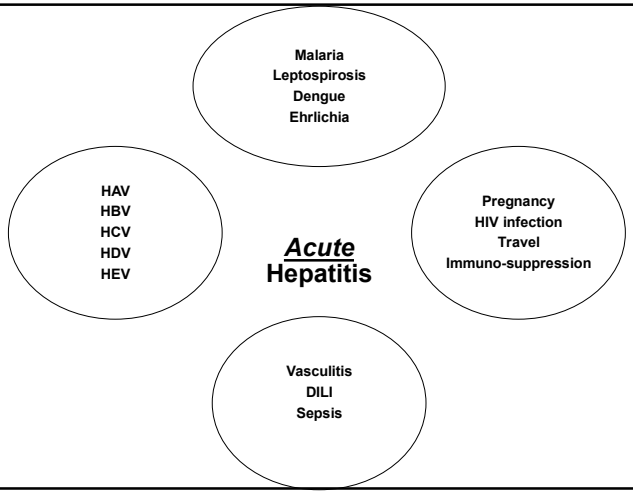
**David Thomas, MD**
Stanhope Bayne-Jones Professor of Medicine
Johns Hopkins Medicine

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- Data and Safety Monitoring Board: Merck and Rho
- Advisory Board: Excision Bio




## Question #1

- 18-year-old with jaundice presents with 5 days of headache, fever, diarrhea, vomiting, chest pain
- PMH – Open fractures of all metatarsals with pins x 3mo
- SH – home tattoos; lives with parents and pregnant girlfriend; dogs and rats; swam in freshwater dam 1 week before symptom onset; cuts grass; multiple tick bites; Maryland

Courtesy E. Prochaska, MD



©2026 Infectious Disease Board Review, LLC

## Question #1

- T 39.4; BP 118/62 (then on pressors); P 91; 97% RA
- Icteric, non-injected, no murmurs
- Diffuse petechial rash; purple macules on ankle
- WBC 11,740 (92.4 P, 0.8B, 2% L); Hb 14.2; Plt 47,000
- Creatinine 0.9-3.4; CRP 10.1; Tbili 4.1 (direct 3.7); ALT/AST 26/53; CK 887
- HIV Ab neg; SARS-CoV-2 PCR neg; Monospot - neg

Courtesy E. Prochaska, MD

## Question #1

### What is the cause of his illness?

A. Acute hepatitis A
*B. Babesia microti*
C. Tularemia
*D. Leptospira icterohaemorrhagiae*
E. HSV

Courtesy E. Prochaska, MD

## Question #1

### What is the cause of his illness?

A. Acute hepatitis A
*B. Babesia microti*
C. Tularemia
***D. Leptospira icterohaemorrhagiae****
E. HSV

Courtesy E. Prochaska, MD

## Leptospirosis

1. Exposure to fresh water (e.g., rafting in Hawaii/Costa Rico or triathlon) OR rats (Baltimore)


©2026 Infectious Disease Board Review, LLC

## Leptospirosis

2. Bilirubin fold change > ALT



## Leptospirosis

3. Biphasic possible and systemic findings (conjunctival suffusion, kidney, skin, muscle, lungs, liver)

   DDx: liver (ALT) and muscle (CPK): lepto, flu, adeno, EBV, HIV, malaria, Rickettsia/Ehrlichiosis, tularemia, TSS, coxsackie, vasculitis

## Leptospirosis

4. Diagnosis:

   - PCR most useful (urine pos longer)
   - Serology late

## Question #2

### Acute Hepatitis in Pakistan

- 52-year-old male has malaise, jaundice and RUQ pain
- One month ago, he returned from 1 month visit with family in NW Pakistan. Typical family exposures in village. No known bites. Mostly inside due to rain. No alcohol or sexual exposures
- Grew up in Pakistan until 24 yrs; unsure about vaccinations.
- On losartan for HTN and metformin for diabetes
- T 100.2 F; jaundiced; RUQ tender. ALT 1245 IU/ml; TB 3.2 mg/dl; WBC 3.2k nl differential; HIV neg


©2026 Infectious Disease Board Review, LLC

## Question #2

### Which test result is most likely positive?

A. Andes virus PCR
B. IgM anti-HEV
C. IgM anti-HAV
D. Schistosomiasis “liver” antigen
E. 16S RNA for Rickettsial organism

## Question #2

### Which test result is most likely positive?

A. Andes virus PCR
**B. IgM anti-HEV***
C. IgM anti-HAV
D. Schistosomiasis “liver” antigen
E. 16S RNA for Rickettsial organism

## Prior HAV Infection/Protection is Near Universal in Persons Residing in LMIC

**HAV Seroprevalence by Age in 2005**

| Age Group | Southeast Asia | East sub-Saharan Africa | High-income North America |
|---|---|---|---|
| 1-4 | 20 | 98 | 0 |
| 5-9 | 35 | 100 | 0 |
| 10-14 | 35 | 100 | 5 |
| 15-19 | 56 | 100 | 11 |
| 20-24 | 67 | 100 | 16 |
| 25-34 | 79 | 100 | 22 |
| 35-44 | 88 | 100 | 29 |
| 45-54 | 96 | 100 | 37 |
| 55-64 | 100 | 100 | 47 |
| 65-74 | 100 | 100 | 56 |
| 75-84 | 100 | 100 | 68 |
| 85+ | 100 | 100 | 79 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jacobsen Vaccine 2010

## Acute Hepatitis E
### Epidemiologic Clues

- Outbreaks: contaminated water and flooding in SE Asia/Africa
- Sporadic: undercooked meat (**BOAR**, deer, etc.)
- USA: endemic rare, genotype 3, IgG serology positive far more than can be explained by cases
  - Can be hard to interpret



©2026 Infectious Disease Board Review, LLC

## Acute Hepatitis E
### Clinical Clues

- Fatalities in pregnant women
- GBS and neurologic manifestations (vs other hep viruses); pancreatitis
- Diagnosis: RNA PCR; IgM anti-HEV
- Treatment: ribavirin for chronic
- Vaccine in China

## Acute Hepatitis at ID Week

- 42-year-old homeless male approaches a group of ID fellows attending ID Week in San Diego
- One fellow noticed jaundice and suggested he seek medical testing.

**With what diagnosis was the fellow most concerned?**

## Question #3

**With what diagnosis was the fellow most concerned?**

A. HAV
B. HBV
C. Delta
D. HCV
E. HEV

## Question #3

**With what diagnosis was the fellow most concerned?**

**A. HAV***
B. HBV
C. Delta
D. HCV
E. HEV


©2026 Infectious Disease Board Review, LLC

## Hepatitis A: Key Epidemiologic Clues: People, Places and Foods

Homelessness and Hepatitis A—San Diego County, 2016–2018

Corey M. Peak,[1,2,3] Sarah S. Stous,[2] Jessica M. Healy,[4] Megan G. Hofmeister,[5] Yulin Lin,[5] Sumathi Ramachandran,[5] Monique A. Foster,[5] Annie Kao,[2] and Eric C. McDonald[2]

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]County of San Diego Health and Human Services Agency, and [3]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, San Diego, California; and Divisions of [4]Foodborne, Waterborne, and Environmental Diseases, and [5]Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

Morbidity and Mortality Weekly Report (*MMWR*)

CDC > MMWR

*Notes from the Field*: Increase in Reported Hepatitis A Infections Among Men Who Have Sex with Men — New York City, January–August 2017

*Weekly* / September 22, 2017 / 66(37);999-1000

## Hepatitis A: Key Epidemiologic Clues: People, Places and Foods

Homelessness and Hepatitis A—San Diego County, 2016–2018

Corey M. Peak,[1,2,3] Sarah S. Stous,[2] Jessica M. Healy,[4] Megan G. Hofmeister,[5] Yulin Lin,[5] Sumathi Ramachandran,[5] Monique A. Foster,[5] Annie Kao,[2] and Eric C. McDonald[2]

[1]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]County of San Diego Health and Human Services Agency, and [3]Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, San Diego, California; and Divisions of [4]Foodborne, Waterborne, and Environmental Diseases, and [5]Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia

CNN Health | Life, But Better | Fitness | Food | Sleep | Mindfulness | More | Watch | Listen | Live TV | Subscribe

HEALTH • 5 MIN READ

**There is a hepatitis A outbreak in LA County. Why you need to know**

UPDATED MAY 15, 2025

By Katia Hetter

## Hepatitis A: Key Epidemiologic Clues: People, Places and Foods

Multistate Outbreak of Hepatitis A Linked to Frozen Strawberries - Current Case Count Map and Table



Case Count as of December 13, 2016

| State | Case Count |
|---|---|
| Arkansas | 1 |
| California | 1 |
| Maryland | 12 |
| New York | 5 |
| North Carolina | 4 |
| Oregon | 1 |
| Virginia | 109 |
| West Virginia | 7 |
| Wisconsin | 3 |
| Grand Total | 143 |

Outbreak of hepatitis A in Hawaii linked to raw scallops

Posted August 19, 2016 5:00 PM ET

Outbreak

The Hawaii Department of Health (HDOH) is investigating an outbreak of hepatitis A in its state. For the latest case count and investigation findings, visit the HDOH outbreak investigation website. On August 15, 2016, HDOH identified raw scallops served at Genki Sushi restaurants on the islands of Oahu and Kauai as a likely source of the ongoing outbreak.

CDC and the U.S. Food and Drug Administration (FDA) are assisting HDOH with its investigation. At this time, CDC is not aware of any hepatitis A virus infections in other states linked to the Hawaii outbreak. CDC continues to monitor for illnesses in other states.






## Hepatitis A: Key Clinical Clues

- Clinical syndrome
  - Fulminant on HCV
  - Relapsing: symptoms/jaundice recur <12 mo



©2026 Infectious Disease Board Review, LLC

## Vaccination to Prevent Hepatitis A

- **Pre-exposure: vaccinate**
  - HOW: Inactivated vaccines USA (HAVRIX,VAQTA )(TWINRIX)
  - WHOM: All children 1-18 yrs receive hepatitis A vaccine (since 2006)
  - HIV, HCV or HBV positive persons/chronic liver disease/homeless/MSM/PWID/Travelers/adoptee exposure
- **Post-exposure: vaccinate or possibly IG if:** ☆
  - > 40 years or immunosuppressed then IG is 'preferred'

Victor NEJM 2007; MMWR July 3 2020; MMWR October 19, 2007 / 56(41);1080-1084

## Vaccination Works to Prevent Hepatitis A

**Up to 14 Days After Exposure in Healthy Young Adults**

| End Points | Per-Protocol Population | | Modified Intention-to-Treat Population† | |
|---|---|---|---|---|
| | Vaccine Group (N=568) | Immune Globulin Group (N=522) | Vaccine Group (N=740) | Immune Globulin Group (N=674) |
| | *number (percent)* | | | |
| **Clinical** | | | | |
| Primary | | | | |
| Any symptom plus IgM-positive and ALT ≥ twice ULN | 25 (4.4) | 17 (3.3) | 26 (3.5) | 18 (2.7) |
| Secondary | | | | |
| Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡ | 29 (5.1) | 19 (3.6) | 30 (4.1) | 20 (3.0) |
| Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR | 18 (3.2) | 12 (2.3) | 19 (2.6) | 12 (1.8) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Victor NEJM 2007

## Acute Viral Hepatitis B Clues

- Most linked to sex, drugs
  - Nosocomial (finger stick devices, etc)
  - Most transmissible (HBV>HCV>HIV)
- Clinical
  - Acute immune complex disease possible
  - Diagnose: IgM anti-core, HBsAg and HBV DNA
  - New infection vs reactivation (both can be IgM pos)

## Prevention by Vaccine +/ HBIG

- Pre-exposure:
  - HBV vaccine (Engerix, Recombivax, Heplisav-B, Pediarix, Twinrix)
- Post-exposure:
  - Vaccinated and anti-HBs >10 ever, done*
  - No history of vaccine and/or anti-HBs <10 IU, HBIG and vaccinate
  - Infant: birth dose vaccine, HBIG, maternal TDF**

*May be exception for patients with immunosuppression like HIV or dialysis;**TDF if maternal HBV DNA >200,000 IU/ml

Schillie MMWR 2018



©2026 Infectious Disease Board Review, LLC

## Acute Viral Hepatitis Delta Will Be with HBV

- HDV
  - HBV co-infection
    - Fulminant with acute HBV
  - HBV superinfection
    - Acute hepatitis in someone with chronic HBV
  - Test for HDV RNA (antibodies for routine screen)

## Acute Viral Hepatitis C Clues

- HCV
  - IDU link (hepatitis in Appalachia)
  - HIV pos MSM ☆
  - Acute RNA pos but AB neg or pos
  - 60-80% persist: more in men, HIV pos, African ancestry, INFL4 gene intact

Cox CID 2005

## Question #4

### Hepatitis and Confusion After Camping

- 65 y/o with T2DM, HTN and memory impairment presents with acute confusion and cough
- 1 week PTA: lethargy and confusion during camping that progressed until found 'down' and incontinent
- Avid outdoors; lives and camps in rural PA; frequent tick and mosquito bites, SP doxy x1 one month earlier; no animals
- T 37.1, 95% on 3L; oriented x2; no rash; RUQ tender

Courtesy Jillian Peters

## Question #4

| | OSH Presentation | JHH ICU |
|---|---|---|
| **WBC** | 12.4 | 11.4 |
| **Hemoglobin** | 10.6 | 8.0 |
| **Platelets** | 116 | 42 |
| **Na** | 132 | 142 |
| **Cr** | 5.4 | 3.0 |
| **AST** | 6590 | 564 |
| **ALT** | 3646 | 671 |
| **Alk Phos** | 83 | 228 |
| **T. Bili** | 1.3 | 9.0 |
| **Lactate** | 9.3 | 6.8 |
| **Ammonia** | 260 | 82 |

- INR 1.6
- APTT 45.6
- D-dimer >30
- Fibrinogen 110
- LDH 1390
- Ferritin: 25,299
- CK 14,000
- Chest CT: bilat UL consolidation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Courtesy Jillian Peters



©2026 Infectious Disease Board Review, LLC

## Question #4

**What agent caused this illness?**

*A. Leptospira icterohaemorrhagiae*
B. Hepatitis A
C. EBV
*D. A. Phagocytophilum*
E. Hepatitis G (GB virus C)

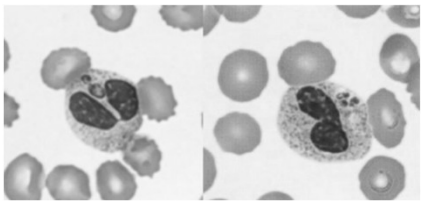
## Question #4

**What agent caused this illness?**

*A. Leptospira icterohaemorrhagiae*
B. Hepatitis A
C. EBV
***D. A. Phagocytophilum****
E. Hepatitis G (GB virus C)

## Hepatitis and Confusion After Camping

| | |
|---|---|
| A.Phagocytophilum,DNA,PCR | DETECTED ! |
| Comment: REFERENCE RANGE: NOT DETECTED | |
| A.Phagocytophilum Ab IgG <1:64 | 1:64 ^ |
| A.Phagocytophilum Ab Interp. | SEE BELOW |
| Comment: Equivocal: Due to a low/negative IgG and a positive IgM, the presence of a recent/current infection should be confirmed by running acute and convalescent sera in parallel and an increasing IgG value detected. | |
| A.Phagocytophilum Ab IgM <1:20 | 1:160 ^ |
| E.Chaffeensis Ab IgG <1:64 | <1:64 |



Courtesy Jillian Peters

## Hepatitis with Bacterial Infections

1. Think Rickettsia/Ehrlichia/Anaplasma with exposure, low PMN, modest ALT, and especially low platelets


©2026 Infectious Disease Board Review, LLC

## Hepatitis with Bacterial Infections

2. When more cholestatic but still with liver, lung, renal, skin, CNS disease consider coxiella burnetti and spirochetes (syphilis and lepto) vs. Rickettsia/Ehrlichia/Anaplasma

## Hepatitis with Bacterial Infections

3. Hepatitis F or G are always WRONG answers

## Question #5

### Hepatitis in Pregnancy

- 37-year-old 35 weeks gestation with 1 week fever, chills, abd pain.
- Pre-term labor and healthy baby delivered C-section
- Rapid deterioration of mom: fever with severe myalgia and low BP
- Plt 143K; Hb 8.6; WBC 6.4K 20% bands; glucose, creat and INR WNL; ALT and AST >2000 IU/ml; BR nl; Fibrinogen NL

Courtesy V Fabre; Allen OB GYN 2005

## Question #5

### What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. Atypical DRESS from antibiotics
D. HSV infection
E. HEV


©2026 Infectious Disease Board Review, LLC

## Question #5

### What is the best diagnosis?

A. HELLP
B. Acute fatty liver of pregnancy
C. Atypical DRESS from antibiotics
**D. HSV infection***
E. HEV

## Hepatitis in Pregnancy

1. Rule out HSV
   - ~50% have muco-cutaneous lesions
   - High mortality without acyclovir

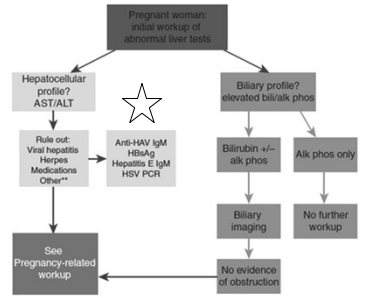



Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

ACOG 2016

## Hepatitis in Pregnancy

2. HELLP
   - HTN and can occur post partum
   - Fibrinogen high vs. sepsis and AFLP

3. AFLP – severe: Abn ALT and TB PLUS- low glucose, incr INR, low fibrinogen; elevated WBC (Swansea criteria)

## Question #6

### Fulminant Hepatitis

- 65-year-old man with Hx of jaundice
- 2 weeks before finished amoxicillin/clavulanate acid for sinusitis
- Hx of HTN on HCTZ and rosuvastatin
- ETOH: 2 drinks per day

- TB24; ALT 162 U/L; AST 97 U/L ALK P 235 U/L
- IgM anti-HAV neg; IgM anti-HBc neg; HCV RNA neg
- RUQ US neg



©2026 Infectious Disease Board Review, LLC

## Question #6

**Which of the following is the most likely cause of hepatitis?**

A. Toxicity from Amox/Clav
B. Alcohol
C. Porphyria flare
D. Leptospirosis
E. Statin

## Question #6

**Which of the following is the most likely cause of hepatitis?**

**A. Toxicity from Amox/Clav***
B. Alcohol
C. Porphyria flare
D. Leptospirosis
E. Statin

## Drug Related Liver Toxicity

Amoxicillin/clavulanate is most common

- Cholestatic or mixed
- Often AFTER stopping
- 1/2500 Rx
- DRB1*1501
- Clavulanate>amoxicillin

| Rank | Agent | Year of FDA Approval | No. (%)† | Major Phenotypes |
|---|---|---|---|---|
| 1 | Amoxicillin–clavulanate | 1984 | 91 (10.1) | Cholestatic or mixed hepatitis |
| 2 | Isoniazid | 1952 | 48 (5.3) | Acute hepatocellular hepatitis |
| 3 | Nitrofurantoin | 1953 | 42 (4.7) | Acute or chronic hepatocellular hepatitis |
| 4 | TMP-SMZ | 1973 | 31 (3.4) | Mixed hepatitis |
| 5 | Minocycline | 1971 | 28 (3.1) | Acute or chronic hepatocellular hepatitis |
| 6 | Cefazolin | 1973 | 20 (2.2) | Cholestatic hepatitis |
| 7 | Azithromycin | 1991 | 18 (2.0) | Hepatocellular, mixed, or cholestatic hepatitis |
| 8 | Ciprofloxacin | 1987 | 16 (1.8) | Hepatocellular, mixed, or cholestatic hepatitis |
| 9 | Levofloxacin | 1996 | 13 (1.4) | Hepatocellular, mixed, or cholestatic hepatitis |
| 10 | Diclofenac | 1988 | 12 (1.3) | Acute or chronic hepatocellular hepatitis |
| 11 | Phenytoin | 1946 | 12 (1.3) | Hepatocellular or mixed hepatitis |
| 12 | Methyldopa | 1962 | 11 (1.2) | Hepatocellular or mixed hepatitis |
| 13 | Azathioprine | 1968 | 10 (1.1) | Cholestatic hepatitis |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019

## Acute Hepatitis Summary

☆ • HEV: flood/travel or boar
☆ • Acute A: vaccine effective
☆ • HIV: acute HCV in MSM
☆ • Low platelet: Ehrlichial, anaplasma or rickettsial
☆ • Find the lepto case (jaundice>hepatitis)!



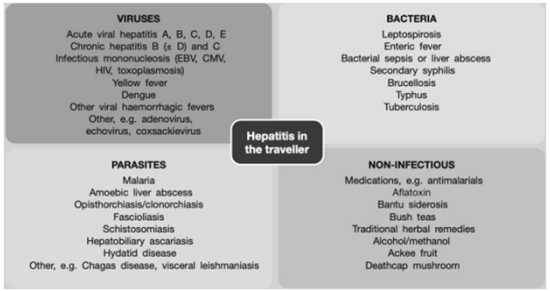
©2026 Infectious Disease Board Review, LLC

**Thanks and good luck!**

**Questions?**
**Dave Thomas: dthomas@jhmi.edu**

## Hepatitis with Travel to Developing Country

**There is a broad differential**




Jones Medicine 2017


©2026 Infectious Disease Board Review, LLC

# Prior HAV Infection/Protection is Near Universal in Persons Residing in LMIC

**HAV Seroprevalence by Age in 2005**

| Age Group | Southeast Asia | East sub-Saharan Africa | High-income North America |
|---|---|---|---|
| 1-4 | 20 | 98 | 0 |
| 5-9 | 35 | 100 | 0 |
| 10-14 | 35 | 100 | 5 |
| 15-19 | 56 | 100 | 11 |
| 20-24 | 67 | 100 | 16 |
| 25-34 | 79 | 100 | 22 |
| 35-44 | 88 | 100 | 29 |
| 45-54 | 96 | 100 | 37 |
| 55-64 | 100 | 100 | 47 |
| 65-74 | 100 | 100 | 56 |
| 75-84 | 100 | 100 | 68 |
| 85+ | 100 | 100 | 79 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Jacobsen Vaccine 2010



©2026 Infectious Disease Board Review, LLC

# Vaccination Works to Prevent Hepatitis A
## Up to 14 Days After Exposure in Healthy Young Adults

| End Points | Per-Protocol Population | | Modified Intention-to-Treat Population† | |
|---|---|---|---|---|
| | Vaccine Group (N=568) | Immune Globulin Group (N=522) | Vaccine Group (N=740) | Immune Globulin Group (N=674) |
| | *number (percent)* | | | |
| **Clinical** | | | | |
| Primary | | | | |
| Any symptom plus IgM-positive and ALT ≥ twice ULN | 25 (4.4) | 17 (3.3) | 26 (3.5) | 18 (2.7) |
| Secondary | | | | |
| Any symptom plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR‡ | 29 (5.1) | 19 (3.6) | 30 (4.1) | 20 (3.0) |
| Jaundice plus IgM-positive and ALT ≥ twice ULN or HAV RNA–positive on PCR | 18 (3.2) | 12 (2.3) | 19 (2.6) | 12 (1.8) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Victor NEJM 2007



©2026 Infectious Disease Board Review, LLC

# Question #4

| | OSH Presentation | JHH ICU |
|---|---|---|
| **WBC** | 12.4 | 11.4 |
| **Hemoglobin** | 10.6 | 8.0 |
| **Platelets** | 116 | 42 |
| **Na** | 132 | 142 |
| **Cr** | 5.4 | 3.0 |
| **AST** | 6590 | 564 |
| **ALT** | 3646 | 671 |
| **Alk Phos** | 83 | 228 |
| **T. Bili** | 1.3 | 9.0 |
| **Lactate** | 9.3 | 6.8 |
| **Ammonia** | 260 | 82 |

- INR 1.6
- APTT 45.6
- D-dimer >30
- Fibrinogen 110
- LDH 1390
- Ferritin: 25,299
- CK 14,000
- Chest CT: bilat UL consolidation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Courtesy Jillian Peters



©2026 Infectious Disease Board Review, LLC

# Hepatitis in Pregnancy

1. Rule out HSV
   - ~50% have muco-cutaneous lesions
   - High mortality without acyclovir

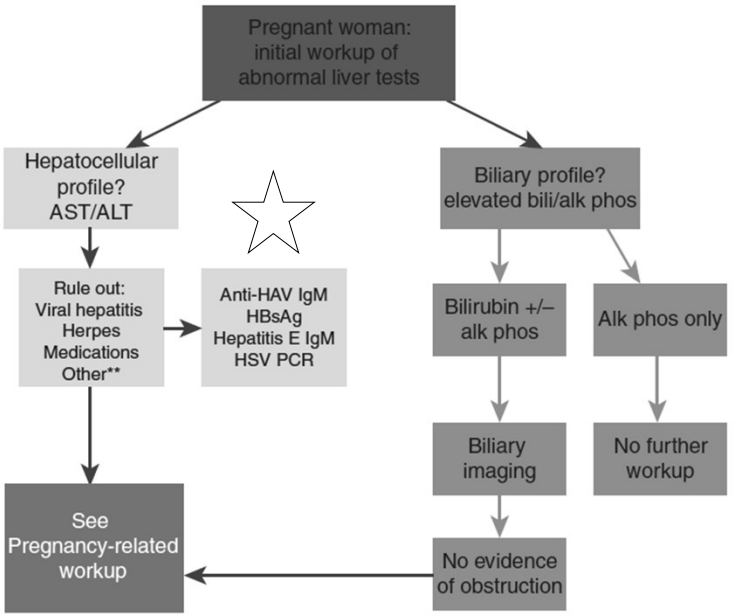



Figure 1. Workup of abnormal liver test in pregnant woman. **Other differential diagnosis to consider if clinically appropriate: AIH, Wilson disease.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

ACOG 2016



©2026 Infectious Disease Board Review, LLC

# Drug Related Liver Toxicity

Amoxicillin/clavulanate is most common

- Cholestatic or mixed
- Often AFTER stopping
- 1/2500 Rx
- DRB1*1501
- Clavulanate>amoxicillin

| Rank | Agent | Year of FDA Approval | No. (%)† | Major Phenotypes |
|---|---|---|---|---|
| 1 | Amoxicillin–clavulanate | 1984 | 91 (10.1) | Cholestatic or mixed hepatitis |
| 2 | Isoniazid | 1952 | 48 (5.3) | Acute hepatocellular hepatitis |
| 3 | Nitrofurantoin | 1953 | 42 (4.7) | Acute or chronic hepatocellular hepatitis |
| 4 | TMP-SMZ | 1973 | 31 (3.4) | Mixed hepatitis |
| 5 | Minocycline | 1971 | 28 (3.1) | Acute or chronic hepatocellular hepatitis |
| 6 | Cefazolin | 1973 | 20 (2.2) | Cholestatic hepatitis |
| 7 | Azithromycin | 1991 | 18 (2.0) | Hepatocellular, mixed, or cholestatic hepatitis |
| 8 | Ciprofloxacin | 1987 | 16 (1.8) | Hepatocellular, mixed, or cholestatic hepatitis |
| 9 | Levofloxacin | 1996 | 13 (1.4) | Hepatocellular, mixed, or cholestatic hepatitis |
| 10 | Diclofenac | 1988 | 12 (1.3) | Acute or chronic hepatocellular hepatitis |
| 11 | Phenytoin | 1946 | 12 (1.3) | Hepatocellular or mixed hepatitis |
| 12 | Methyldopa | 1962 | 11 (1.2) | Hepatocellular or mixed hepatitis |
| 13 | Azathioprine | 1968 | 10 (1.1) | Cholestatic hepatitis |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

http://livertox.nlm.nih.gov; Hoofnagle NEJM 2019



©2026 Infectious Disease Board Review, LLC

Wednesday, August 26, 2026

47

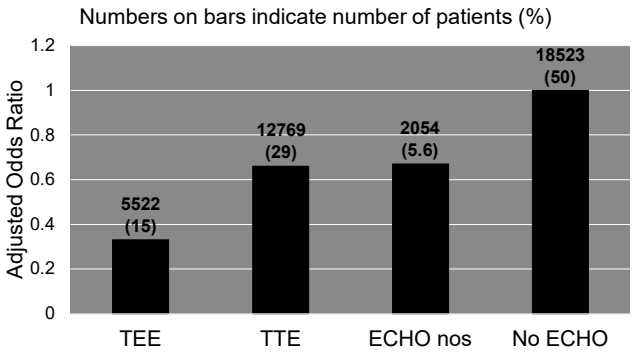
# Staphylococcus Aureus

Henry Chambers, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

## ECHO and Mortality in SAB




TEE= transesophageal ECHO, TTE = transthoracic ECHO, nos = type not specified

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

VAH Study: JAMA Intern Med 177:1489, 2017

## Prediction Scores to Rule-out Endocarditis (and avoid an ECHO) in Patients with S. aureus Bacteremia (SAB)

| POSITIVE (Cutoff >4) | PREDICT (Cutoff ≥2) | VIRSTA (Cutoff ≥3) |
|---|---|---|
| TTP < 9h – 13h (2,3,5)<br>IVDU (3)<br>Vascular phenomena (6)<br>Predisposing heart dis (5) | ICD (2)<br>Pacemaker (3)<br>CA SAB (2)<br>HCA SAB (1)<br>Positive BC > 72h (2) | Emboli (5)<br>Meningitis (5)<br>Intracardiac device (4)<br>Previous IE (3)<br>IVDU (4)<br>Positive BC > 48h (3)<br>CA or HCA SAB (2)<br>Sepsis or septic shock (1)<br>CRP > 190 mg/L (1) |

TTP = time to positivity of blood culture, IVDU = IV drug use, ICD = intracardiac device, CRP = C-reactive protein

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

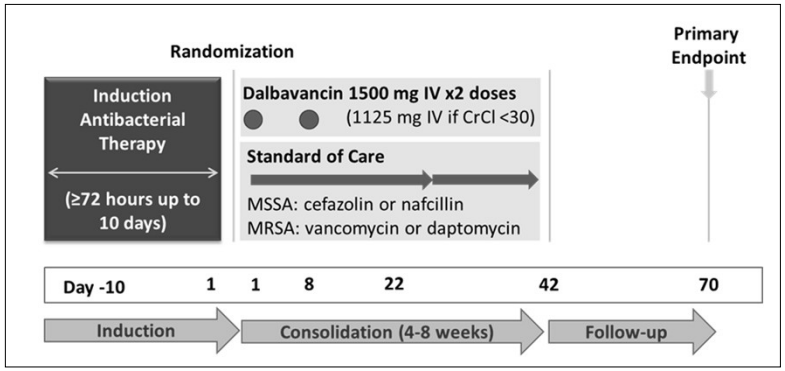
Clin Infect Dis 2022; 74:1442, J Antimicrob Chemother 2022; 77: 2003, J. Clin. Med. 2022; 11: 1502.

## Outcomes

| Outcome Measure | Cefazolin (n=146) | Cloxacillin (n=146) | Δ (95%CI) |
|---|---|---|---|
| Primary | 109 (75%) | 108 (74%) | 1% (-11 to 9) |
| Survival, 90 d | 134 (92%) | 134 (92%) | 0% (-7 to 7) |
| Micro success, d3/5 | 136 (93%) | 135 (92%) | 1% (-6 to 7) |
| No relapse, 90 d | 145 (99%) | 144 (99%) | 1% (-3 to 4) |
| Clinical success, 90 d | 116/144 (81%) | 111/139 (80%) | 1% (-9 to 10) |
| Clinical success, 7 d | 105/142 (74%) | 98/140 (70%) | 4% (-6 to 14) |
| Any SAE | 51 (36%) | 64 (44%) | -9% (-20 to 2) |
| SAE by day 7 | 14 (10%) | 30 (20%) | -11 (-19 to -3) |
| AKI, day 7 | 1/134 (1%) | 15/128 (12%) | -11% (-18 to -6) |
| AKI, end of study Rx | 4/111 (4%) | 17/99 (17%) | -13% (-23 to -6) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Methods: DOTS Study Design




(SOC)

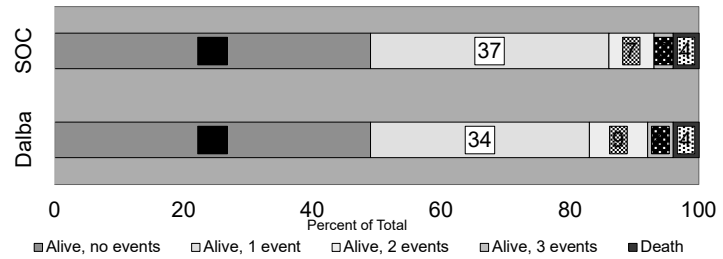
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**47 Staphylococcus aureus**

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Desirability of Outcome Ranking (DOOR) at Day 70




Events: Clinical failure, infectious complication, SAE or AE with study discontinuation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Overview of Studies of Combination Therapy for SAB

| Regimen | Study | Population | Comments | PMID |
|---|---|---|---|---|
| Adjunctive rifampin | RCT | MRSA,MSSA | No benefit | 1929035<br>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<br>31640977<br>31404468 |
| Dapto + fosfomycin | RCT | MRSA | No mortality benefit, ↓ micro failure, ↑ AEs | 32725216<br>32887985 |
| Cefazolin + ertapenem | Obs | MSSA, SAB > 48h | No mortality benefit, SAB duration ↓ by 25h | 38946294 |

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Other Antibiotics for MRSA Infections

| Antibiotic | Indications | Comments |
|---|---|---|
| Linezolid | SSTI, HAP, VAP | Serotonin syndrome; bacteriostatic<br>Bone marrow suppression |
| Ceftaroline | SSTI, CAP | Rash, usual cephalosporin reactions, neutropenia |
| Dalbavancin* | SSTI | Single dose or 2 doses a week apart<br>Lipoglycopeptide, related to teicoplanin |
| Ceftobiprole* | FDA approved SSTI, SAB | Non-inferior to daptomycin in RCT of MSSA and MRSA bacteremia (NEJM 2023;389:1390) |

* Randomized controlled trial data exist for SAB

SSTI = skin and soft tissue infection, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia
CAP = community-acquired pneumonia

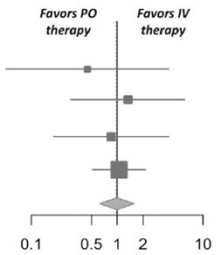
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Meta-Analysis: Oral Therapy of S. aureus Bacteremia

*Treatment Failure*

| Study | PO therapy | IV therapy | RR (95% CI) |
|---|---|---|---|
| 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: $I^2 = 0\%$, $\tau^2 = 0$, $P = .86$




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Clin Infect Dis. 2025;80:29.

**47 Staphylococcus aureus**

*Speaker: Henry Chambers, MD*

©2026 Infectious Disease Board Review, LLC

## Duration of Therapy for SAB

14 days — **UNCOMPLICATED/LOW RISK (~20% of cases)**

- **Sterile blood culture after 2-3 days** (**DOCUMENT!**)
- Fever resolves by day 3
- **Easily removed focus of infection (no DVT)**
- **No metastatic infection**
- **No evidence of endocarditis (negative echo)**
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks + — **COMPLICATED/HIGH RISK**

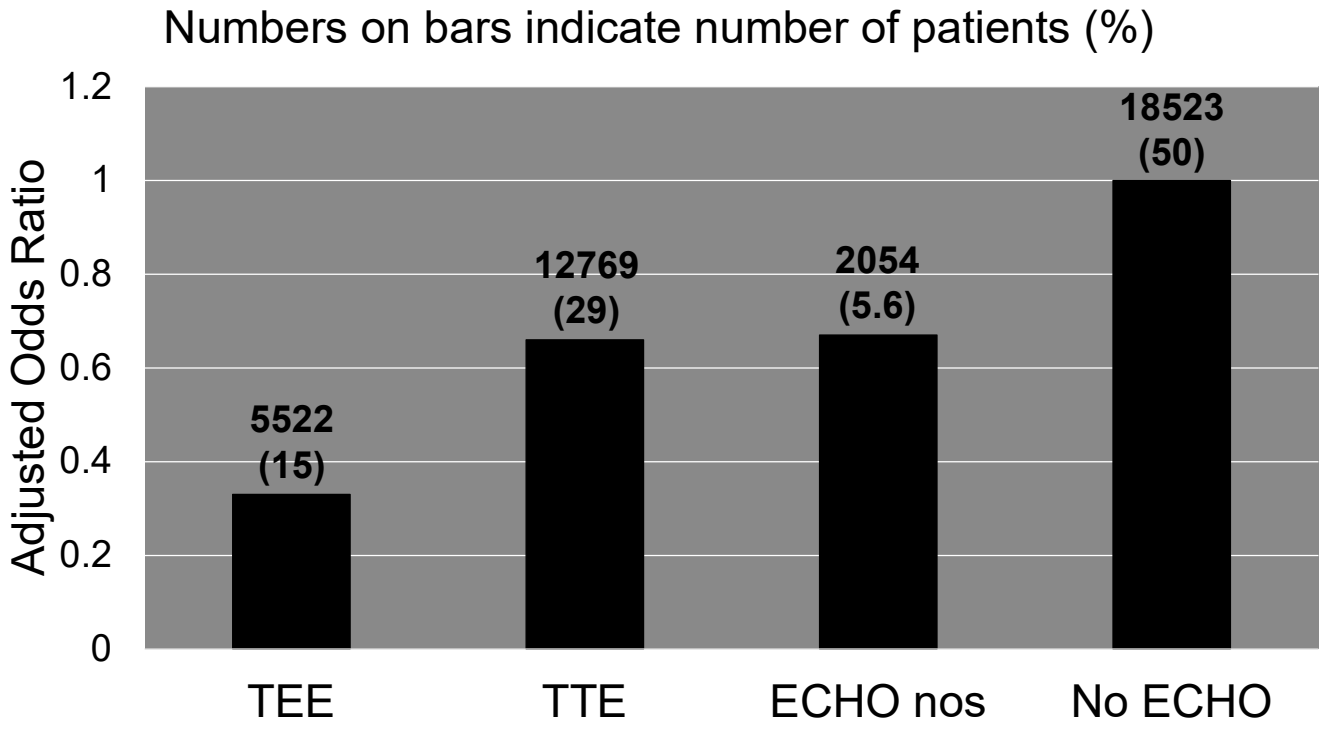
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# ECHO and Mortality in SAB




TEE= transesophageal ECHO, TTE = transthoracic ECHO, nos = type not specified

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

VAH Study: JAMA Intern Med 177:1489, 2017



©2026 Infectious Disease Board Review, LLC

## Prediction Scores to Rule-out Endocarditis (and avoid an ECHO) in Patients with S. aureus Bacteremia (SAB)

| POSITIVE (Cutoff >4) | PREDICT (Cutoff ≥2) | VIRSTA (Cutoff ≥3) |
|---|---|---|
| TTP < 9h – 13h (2,3,5)<br>IVDU (3)<br>Vascular phenomena (6)<br>Predisposing heart dis (5) | ICD (2)<br>Pacemaker (3)<br>CA SAB (2)<br>HCA SAB (1)<br>Positive BC > 72h (2) | Emboli (5)<br>Meningitis (5)<br>Intracardiac device (4)<br>Previous IE (3)<br>IVDU (4)<br>Positive BC > 48h (3)<br>CA or HCA SAB (2)<br>Sepsis or septic shock (1)<br>CRP > 190 mg/L (1) |

TTP = time to positivity of blood culture, IVDU = IV drug use, ICD = intracardiac device, CRP = C-reactive protein

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Clin Infect Dis 2022; 74:1442, J Antimicrob Chemother 2022; 77: 2003, J. Clin. Med. 2022; 11: 1502.



©2026 Infectious Disease Board Review, LLC

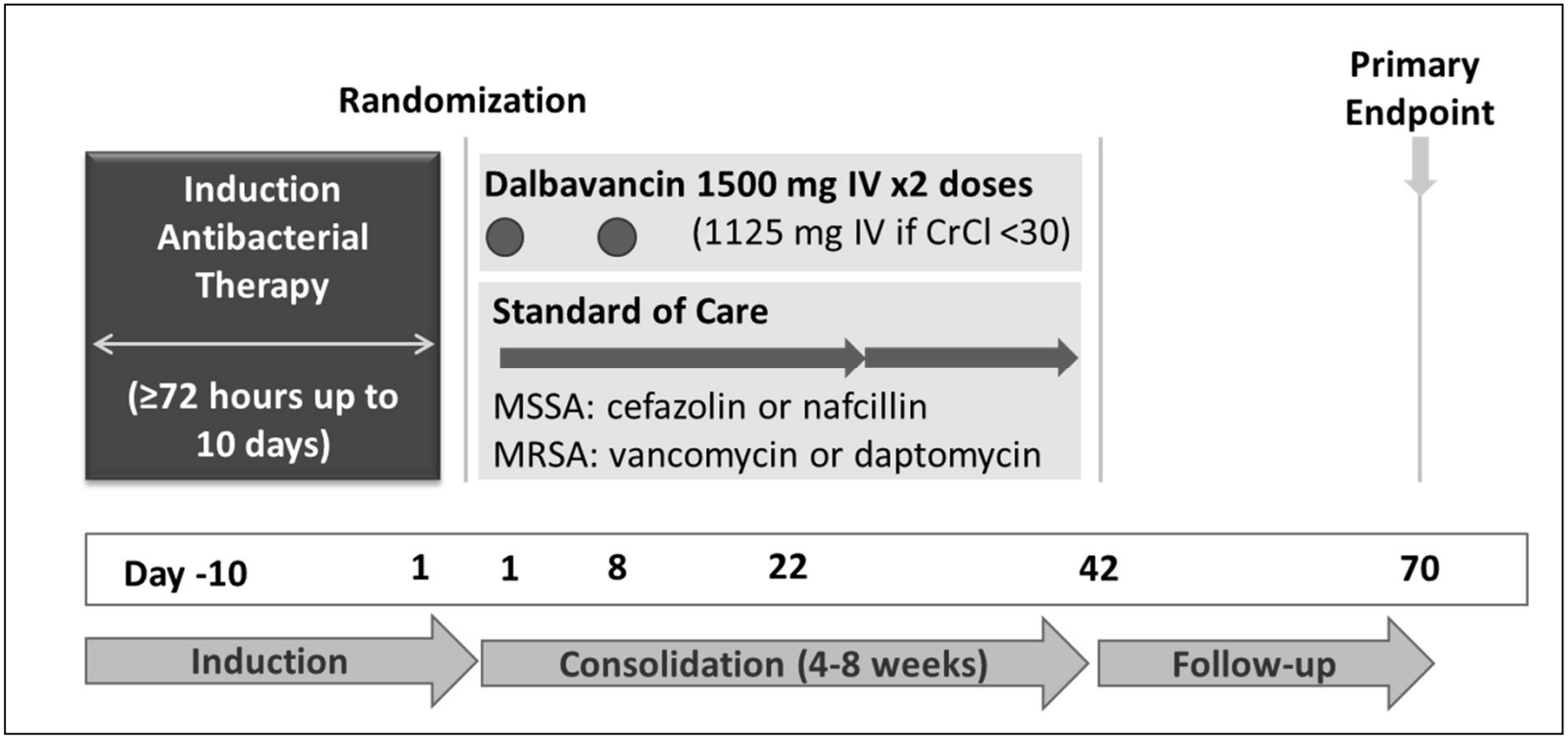
# Outcomes

| Outcome Measure | Cefazolin (n=146) | Cloxacillin (n=146) | Δ (95%CI) |
|---|---|---|---|
| Primary | 109 (75%) | 108 (74%) | 1% (-11 to 9) |
| Survival, 90 d | 134 (92%) | 134 (92%) | 0% (-7 to 7) |
| Micro success, d3/5 | 136 (93%) | 135 (92%) | 1% (-6 to 7) |
| No relapse, 90 d | 145 (99%) | 144 (99%) | 1% (-3 to 4) |
| Clinical success, 90 d | 116/144 (81%) | 111/139 (80%) | 1% (-9 to 10) |
| Clinical success, 7 d | 105/142 (74%) | 98/140 (70%) | 4% (-6 to 14) |
| Any SAE | 51 (36%) | 64 (44%) | -9% (-20 to 2) |
| SAE by day 7 | 14 (10%) | 30 (20%) | -11 (-19 to -3) |
| AKI, day 7 | 1/134 (1%) | 15/128 (12%) | -11% (-18 to -6) |
| AKI, end of study Rx | 4/111 (4%) | 17/99 (17%) | -13% (-23 to -6) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Methods: DOTS Study Design

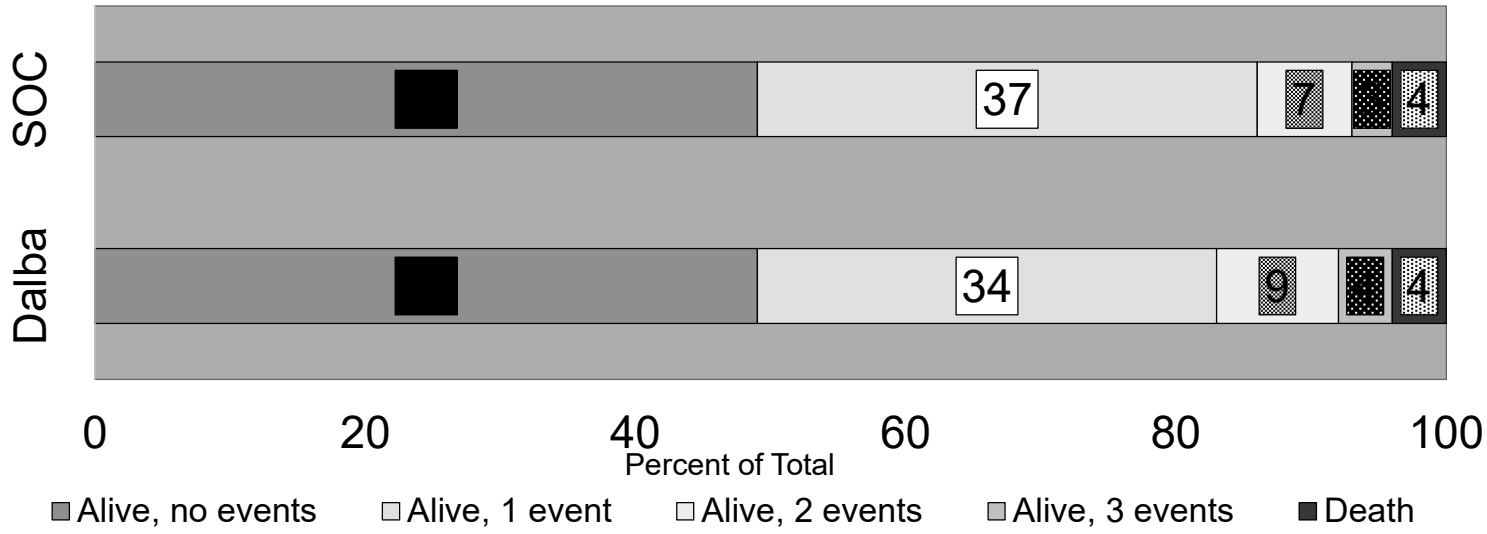



(SOC)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Desirability of Outcome Ranking (DOOR) at Day 70




Events: Clinical failure, infectious complication, SAE or AE with study discontinuation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Overview of Studies of Combination Therapy for SAB

| Regimen | Study | Population | Comments | PMID |
|---|---|---|---|---|
| Adjunctive rifampin | RCT | MRSA,MSSA | No benefit | 1929035<br>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<br>31640977<br>31404468 |
| Dapto + fosfomycin | RCT | MRSA | No mortality benefit, ↓ micro failure, ↑ AEs | 32725216<br>32887985 |
| Cefazolin + ertapenem | Obs | MSSA, SAB > 48h | No mortality benefit, SAB duration ↓ by 25h | 38946294 |

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Other Antibiotics for MRSA Infections

| Antibiotic | Indications | Comments |
|---|---|---|
| Linezolid | SSTI, HAP, VAP | Serotonin syndrome; bacteriostatic<br>Bone marrow suppression |
| Ceftaroline | SSTI, CAP | Rash, usual cephalosporin reactions, neutropenia |
| Dalbavancin* | SSTI | Single dose or 2 doses a week apart<br>Lipoglycopeptide, related to teicoplanin |
| Ceftobiprole* | FDA approved SSTI, SAB | Non-inferior to daptomycin in RCT of MSSA and MRSA bacteremia (NEJM 2023;389:1390) |

* Randomized controlled trial data exist for SAB

SSTI = skin and soft tissue infection, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia
CAP = community-acquired pneumonia

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

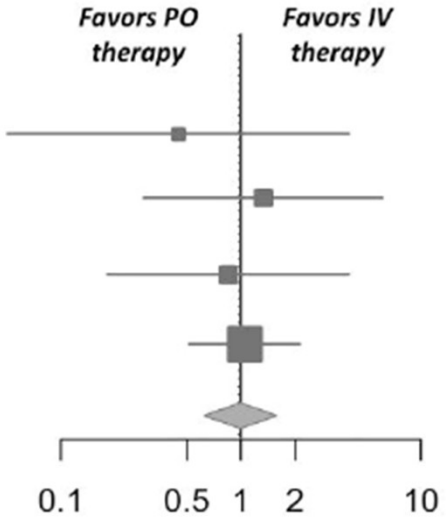


©2026 Infectious Disease Board Review, LLC

# Meta-Analysis: Oral Therapy of S. aureus Bacteremia

| | *Treatment Failure* | | |
|---|---|---|---|
| **Study** | **PO therapy** | **IV therapy** | **RR (95% CI)** |
| 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: $I^2 = 0\%$, $\tau^2 = 0$, $P = .86$




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Clin Infect Dis. 2025;80:29.



©2026 Infectious Disease Board Review, LLC

# Duration of Therapy for SAB

14 days — **UNCOMPLICATED/LOW RISK (~20% of cases)**

- **Sterile blood culture after 2-3 days (DOCUMENT!)**
- Fever resolves by day 3
- **Easily removed focus of infection (no DVT)**
- **No metastatic infection**
- **No evidence of endocarditis (negative echo)**
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks + — **COMPLICATED/HIGH RISK**

- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

**Wednesday, August 26, 2026**

---

**48**

# Chronic Hepatitis

**David Thomas, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

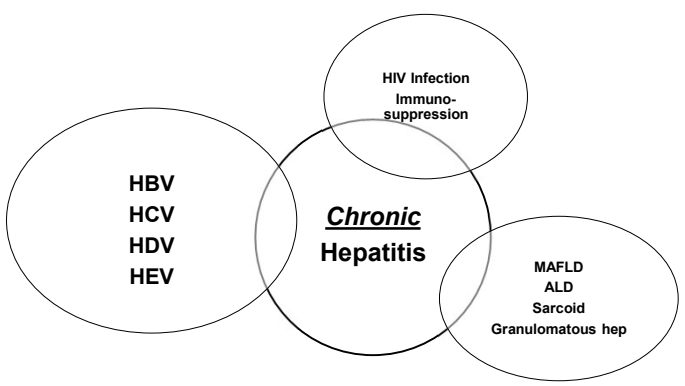
# Chronic Hepatitis

**David Thomas, MD**
**Stanhope Bayne-Jones Professor of Medicine**
**Johns Hopkins Medicine**

9/7/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- Data and Safety Monitoring Board: Merck and Rho
- Advisory Board: Excision Bio




## Question #1

### Case Study: Hepatitis C and a rash

A 44-year-old, anti-HCV and HCV RNA positive man feels bad after a recent alcohol binge. He has a chronic rash on arms that is worse and elevated ALT and AST.



OConnor Mayo Clin Proc 1998



©2026 Infectious Disease Board Review, LLC

## Question #1

### Which is the most likely diagnosis?

A. Cirrhosis due to HCV and alcohol
B. Necrolytic acral erythema
C. Porphyria cutanea tarda
D. Essential mixed cryoglobulinemia
E. Yersinia infection

## Question #1

### Which is the most likely diagnosis?

A. Cirrhosis due to HCV and alcohol
B. Necrolytic acral erythema
**C. Porphyria cutanea tarda***
D. Essential mixed cryoglobulinemia
E. Yersinia infection

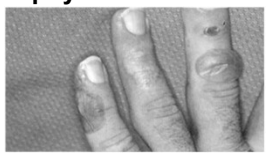
Porphyria Cutanea Tarda Associated with Hepatitis C

Tejesh S. Patel, M.D., and Evgeniva Teterina Mohammed, M.D.

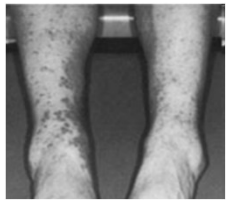


June 10, 2021
N Engl J Med; 384:e86

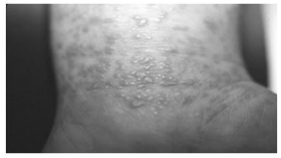
**Porphyria cutanea tarda**



**Cryoglobulin vasculitis**



**Lichen planus**



**Necrolytic acral erythema**

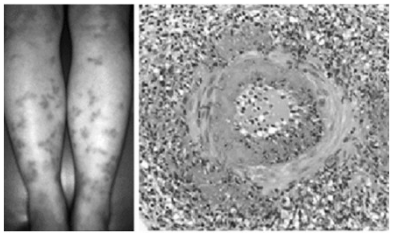


blogspot.com; OConnor Mayo Clin Proc 1998



©2026 Infectious Disease Board Review, LLC

HBV: Polyarteritis nodosa



HCV: Cryoglobulin vasculitis



blogspot.com; OConnor Mayo Clin Proc 1998; Chen Rheum 2014

## Question #2

### What is true regarding testing for HCV antibodies?

A. Testing indicated only for those with risk
B. New 4th generation antibody/ag test sensitive for acute infection
C. Indicated for pregnant women
D. Repeat after cure if new exposures
E. Often falsely negative in persons with HIV

## Question #2

### What is true regarding testing for HCV antibodies?

A. Testing indicated only for those with risk
B. New 4th generation antibody/ag test sensitive for acute infection
**C. Indicated for pregnant women***
D. Repeat after cure if new exposures
E. Often falsely negative in persons with HIV

## IDSA/AASLD Guidelines

Recommendations for One-Time Hepatitis C Testing

| RECOMMENDED | RATING |
|---|---|
| One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older. | I, B |
| One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below). | I, B |
| Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy. | I, B |
| Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below). | IIa, C |
| Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP). | IIa, C |

**RECOMMENDATION** The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

*JAMA*. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## Question #3

### Case Study: HCV antibodies and RNA

- 54-year-old man was anti-HCV pos after routine screen by primary
- RNA also pos; moderate ETOH; otherwise well
- CMP and CBC were normal

### Which of these is most necessary before treatment?

A. HCV genotype
B. HCV 1a resistance test
C. Elastography
D. HBsAg
E. Repeat in 6 months to be sure chronic

## Question #3

### Case Study: HCV antibodies and RNA

- 54-year-old man was anti-HCV pos after routine screen by primary
- RNA also pos; moderate ETOH; otherwise well
- CMP and CBC were normal

### Which of these is most necessary before treatment?

A. HCV genotype
B. HCV 1a resistance test
C. Elastography
D. HBsAg*
E. Repeat in 6 months to be sure chronic




**FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C**

All are tested for HBV

- HBsAg pos: treat per HBV guidelines
- Anti-HBc pos: monitor

Bersoff-Macha Ann Intern Med 2017; Thio and Balagopal CID 2015

## Staging is Needed to Assess for Cirrhosis (But Not Most Urgent)

| Accepted Staging Methods | Not For Routine Staging |
|---|---|
| • Liver biopsy | • Viral load |
| • Blood markers (FIB 4) | • HCV genotype |
| • Elastography | • Ultrasound |
| • Combinations of 1-3 | • CT scan or MRI |

Hcvguidelines.org


©2026 Infectious Disease Board Review, LLC

## HCV NS5 RAS Testing is Uncommonly Recommended

**Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice**

| RECOMMENDED | RATING |
|---|---|
| **Sofosbuvir/velpatasvir**<br>NS5A RAS testing is recommended for treatment-naive persons with genotype 3 infection and cirrhosis being considered for 12 weeks of sofosbuvir/velpatasvir therapy. If the Y93H resistance-associated substitution is present, weight-based ribavirin should be added or another recommended regimen should be used. | I, A |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Wyles, HCVguidelines.org

## Question #4

### Case Study (cont.): HCV antibodies and RNA

- HBsAg neg; anti-HBc pos
- Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis
- Genotype 1a
- Ultrasound ok

**Which can you NOT say is true of treatment?**

A. Reduces risk of reinfection
B. Reduces risk of death
C. Reduces risk of HCC
D. Reduces risk of liver failure

## Question #4

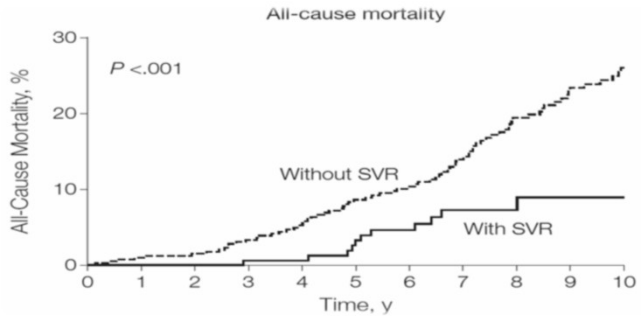
### Case Study (cont.): HCV antibodies and RNA

- HBsAg neg; anti-HBc pos
- Elastography (17.3 kPa) and Fib-4 (5.5) consistent with cirrhosis
- Genotype 1a
- Ultrasound ok

**Which can you NOT say is true of treatment?**

**A. Reduces risk of reinfection***
B. Reduces risk of death
C. Reduces risk of HCC
D. Reduces risk of liver failure

## SVR Reduces Clinical Outcomes




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.



©2026 Infectious Disease Board Review, LLC

## Question #5

### Which is true of initial HCV treatment?

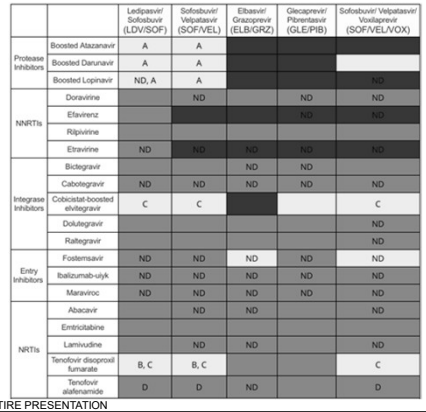
1. Avoid sofosbuvir if renal insufficiency
2. Avoid glecaprevir/pibrentasvir if compensated cirrhosis
3. Avoid glecaprevir if on boosted PI
4. Avoid sofosbuvir/ledipasvir if genotype 1
5. Prolong treatment in person with HIV

## Question #5

### Which is true of initial HCV treatment?

1. Avoid sofosbuvir if renal insufficiency
2. Avoid glecaprevir/pibrentasvir if compensated cirrhosis
3. **Avoid glecaprevir if on boosted PI***
4. Avoid sofosbuvir/ledipasvir if genotype 1
5. Prolong treatment in person with HIV

## HCV-HIV ART Drug Interactions



| | | Ledipasvir/ Sofosbuvir (LDV/SOF) | Sofosbuvir/ Velpatasvir (SOF/VEL) | Elbasvir/ Grazoprevir (ELB/GRZ) | Glecaprevir/ Pibrentasvir (GLE/PIB) | Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX) |
|---|---|---|---|---|---|---|
| Protease Inhibitors | Boosted Atazanavir | A | A | | | |
| | Boosted Darunavir | A | A | | | |
| | Boosted Lopinavir | ND, A | A | | | ND |
| NNRTIs | Doravirine | | ND | | ND | ND |
| | Efavirenz | | | | ND | ND |
| | Rilpivirine | | | | | |
| | Etravirine | ND | ND | ND | ND | ND |
| Integrase Inhibitors | Bictegravir | | | ND | ND | |
| | Cabotegravir | ND | ND | ND | ND | ND |
| | Cobicistat-boosted elvitegravir | C | C | | | C |
| | Dolutegravir | | | | | ND |
| | Raltegravir | | | | | ND |
| Entry Inhibitors | Fostemsavir | ND | ND | ND | ND | ND |
| | Ibalizumab-uiyk | ND | ND | ND | ND | ND |
| | Maraviroc | ND | ND | ND | ND | ND |
| NRTIs | Abacavir | | ND | ND | | ND |
| | Emtricitabine | | | | | |
| | Lamivudine | | ND | ND | | ND |
| | Tenofovir disoproxil fumarate | B, C | B, C | | | C |
| | Tenofovir alafenamide | D | D | ND | | D |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

www.hcvguidelines.com

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] | 8 weeks | I, B |

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

## HCV Treatment Summary

- Test and treat (and stage)
- Two pangenotypic regimens: SOF/VEL and G/P
- **Watch for HBV relapse at week 8 if HBsAg pos**
- No change for HIV (avoid drug interactions), renal insufficiency, acute infection
- Compensated cirrhosis same for G/P and SOF-based except GT3 with resistance

## Hepatitis B: 2023 Testing Recs for USA

**Universal hepatitis B virus (HBV) screening**
- HBV screening at least once during a lifetime for adults aged ≥18 years (new recommendation)
- During screening, test for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and total antibody to HBcAg (total anti-HBc) (new recommendation)

**Screening pregnant persons**
- HBV screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing*
- Pregnant persons with a history of appropriately timed triple panel screening and without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening) only need HBsAg screening

**Risk-based testing**
- Testing for all persons with a history of increased risk for HBV infection, regardless of age, if they might have been susceptible during the period of increased risk†
- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposures, while risk for exposures persists†

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

MMWR March 10, 2023

## Evaluation of Persons with CHB

- HIV, HBV DNA, anti-HDV, HBeAg
- Genotype if IFN considered; q HBsAg is new test
- Stage (liver enzymes and/or elastography or biopsy)
- Renal status
- US to r/o HCC
  - Cirrhosis: all
  - Asian: male 40; female 50
  - African: 25-30

## Quantitative Surface Antigen

- Reflects both integrated and cccDNA
- Independent predictor of HCC and cure
- Eligibility for bepiroversin
- Not used for initial screening
- False pos caused by vaccination within 14d



©2026 Infectious Disease Board Review, LLC

## Question #6

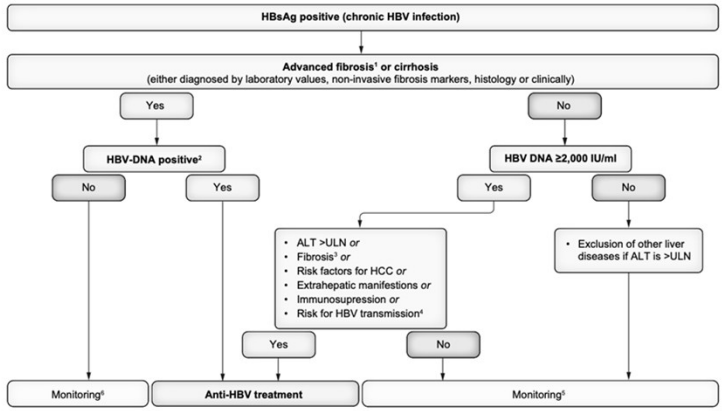
### After HBV Testing, Which Requires Treatment?

| | Age (yrs), clinical | DNA (IU/ml) | ALT (IU/ml) | HBsAg | HBeAg | Anti-HBs | Anti-HBc |
|---|---|---|---|---|---|---|---|
| A. | 41, asymptomatic | 5600 | 78 | Pos | Neg | Neg | Pos |
| B. | 51, asymptomatic | Neg | 48 | Neg | Neg | Neg | Pos |
| C. | 21, born SEA | 8,200,000 | 18 | Pos | Pos | Neg | Pos |
| D. | 62, RA on hydroxy chloroquine | Neg | 34 | Neg | Neg | Neg | Pos |
| E. | 19, student | Neg | 18 | Neg | Neg | Pos | Neg |

## Question #6

### After HBV Testing, Which Requires Treatment?

| | Age (yrs), clinical | DNA (IU/ml) | ALT (IU/ml) | HBsAg | HBeAg | Anti-HBs | Anti-HBc |
|---|---|---|---|---|---|---|---|
| A. | **41, asymptomatic*** | **5600** | **78** | **Pos** | **Neg** | **Neg** | **Pos** |
| B. | 51, asymptomatic | Neg | 48 | Neg | Neg | Neg | Pos |
| C. | 21, born SEA | 8,200,000 | 18 | Pos | Pos | Neg | Pos |
| D. | 62, RA on hydroxy chloroquine | Neg | 34 | Neg | Neg | Neg | Pos |
| E. | 19, student | Neg | 18 | Neg | Neg | Pos | Neg |




EASL J Hepatol 2025; AASLD 2025; WHO 2024

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## HBV Treatment – Simple Version

- If HBV DNA detected and person wants treatment, use ETV, TAF, TDF, or pegIFN
  - HIV treat all
  - Cirrhosis treat all
  - Treatment is indefinite duration
  - Lower confidence of benefit if HBV DNA <2000 IU and/or nl ALT
  - Risk of reactivation when treatment stopped (low)


©2026 Infectious Disease Board Review, LLC

## Treatment of HBV Changes with Renal Insufficiency

- **GFR 30-60 mL/min/1.73 m$^2$:** TAF 25 mg preferred
- **GFR <30-10:** TAF 25mg OR entecavir 0.5 mg q 3d
- **GFR <10 no dialysis:** entecavir 0.5 mg
- **Dialysis:** TDF 300mg/wk PD or entecavir 0.5mg/wk or TAF 25mg PD

## HIV/HBV Coinfected Need Treatment for Both

- All are treated and tested for both
- HBV-active ART
- Entecavir less effective if LAM exposure
- **Watch switch from TAF- or TDF-containing regimen to CAB/RIL or DTG/RPV or XTC when HBsAg pos**
  - **HBV reactivation ~1% if just anti-HBc without HBsAg (Cenix and Opera cohorts, CROI 2026)**

## Question #7

### Case Study: Hepatitis serology in the oncology suite

- You are called about 62-year-old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non-Hodgkins lymphoma.
- Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

### What do you recommend?

A. Hold rituximab
B. Hold prednisone
C. Entecavir 0.5 mg
D. HCV PCR

## Question #7

### Case Study: Hepatitis serology in the oncology suite

- You are called about 62-year-old Vietnamese scientist who is in oncology suite where he is about to get R-CHOP for Non-Hodgkins lymphoma.
- Baseline labs: normal AST, ALT, and TBili. Total HAV detectable; anti-HBc pos; HBsAg neg; anti-HCV neg.

### What do you recommend?

A. Hold rituximab
B. Hold prednisone
**C. Entecavir 0.5 mg***
D. HCV PCR


©2026 Infectious Disease Board Review, LLC

## Rituximab, High-dose Prednisone, and BM Transplant High Risk for HBV Reactivation

- If HBsAg pos, prophylaxis *always* recommended
- If anti-HBc pos but HBsAg neg, prophylaxis still recommended with high-risk exposures (anti-CD20, high dose Pred, BM tx)
- Use TAF or ETV for 6-12 mo after dc immunosuppression (12 for anti-CD20)

AASLD Terrault Hepatology 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection

**Figure 2. Functional Cure at Week 72 and Key Secondary Outcome, According to Baseline HBsAg Level.**

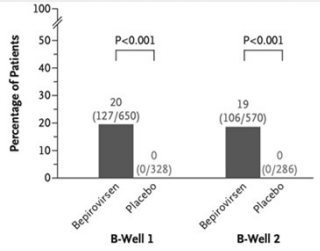
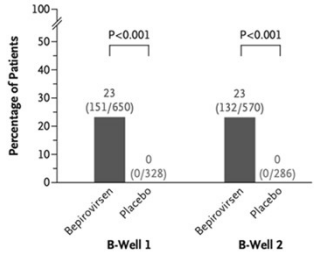



**Figure 3. Discontinuation of NA and HBV DNA below LLOQ or Not Detected at Week 72, According to Baseline HBsAg Level.**




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Hou NEJM 2026

## A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

Wedemeyer H. et al. DOI: 10.1058/NJEMoa2213429

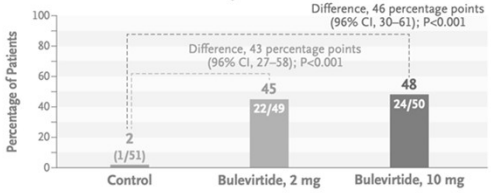
FDA NEWS RELEASE

### FDA Approves First Treatment for Chronic Hepatitis Delta Virus (HDV) Infection

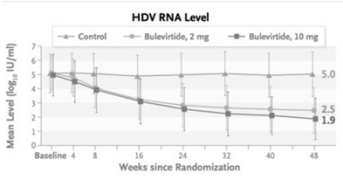
**For Immediate Release:** May 22, 2026

Today, the U.S. Food and Drug Administration approved Hepcludex (bulevirtide-gmod)

**Combined Response at Week 48**




**HDV RNA Level**




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Question #8

### Case Study: Boaring chronic hepatitis in a transplant recipient

- 51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid. Hunts wild boar in Texas
- HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

### Which test is most likely abnormal?

A. HEV PCR
B. HCV IgM
C. Tacrolimus level
D. Adenovirus PCR
E. Delta RNA PCR



©2026 Infectious Disease Board Review, LLC

## Question #8

### Case Study: Boaring chronic hepatitis in a transplant recipient

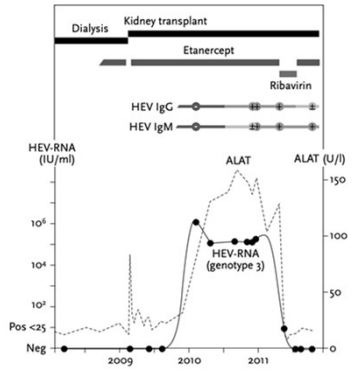
- 51 y/o HTN, and ankylosing spondylitis s/p renal transplant presents with elevated liver enzymes. Pred 20/d; MMF 1g bid; etanercept 25mg twice/wk; tacro 4mg bid. Hunts wild boar in Texas
- HBsAg neg, anti-HBs pos, anti-HBc neg; anti-HCV neg; HCV RNA neg; CMV IgG neg; EBV neg; VZV neg. ALT 132 IU/ml, AST 65 IU/ml; INR 1. ALT and AST remained elevated; HBV, HCV, HAV, CMV, EBV serologies remain neg.

### Which test is most likely abnormal?

**A. HEV PCR***
B. HCV IgM
C. Tacrolimus level
D. Adenovirus PCR
E. Delta RNA PCR

## Chronic HEV in Transplant Recipient

- Europe (boar)
- Can cause cirrhosis
- Tacrolimus associated
- Ribavirin may be effective




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Barrague Medicine 2017

## Chronic Hepatitis for the Boards Summary

☆ • HCV-associated conditions: PCT or cryoglobulinemia
☆ • HCV: HBV reactivation or drug interaction
☆ • HBV: reactivation post rituximab
☆ • HEV: chronic in transplant patient

## Thanks and Good Luck on the Test!

**Questions:**


- Dave Thomas
  - dthomas@jhmi.edu





©2026 Infectious Disease Board Review, LLC

# IDSA/AASLD Guidelines

| Recommendations for One-Time Hepatitis C Testing | |
|---|---|
| RECOMMENDED | RATING |
| One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years or older. | I, B |
| One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below). | I, B |
| Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy. | I, B |
| Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below). | IIa, C |
| Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP). | IIa, C |

**RECOMMENDATION** The USPSTF recommends screening for HCV infection in adults aged 18 to 79 years. (B recommendation)

*JAMA*. doi:10.1001/jama.2020.1123
Published online March 2, 2020.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# HCV NS5 RAS Testing is Uncommonly Recommended

| Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice | |
|---|---|
| RECOMMENDED | RATING ⓘ |
| **Sofosbuvir/velpatasvir**<br>NS5A RAS testing is recommended for treatment-naive persons with genotype 3 infection and cirrhosis being considered for 12 weeks of sofosbuvir/velpatasvir therapy. If the Y93H resistance-associated substitution is present, weight-based ribavirin should be added or another recommended regimen should be used. | I, A |

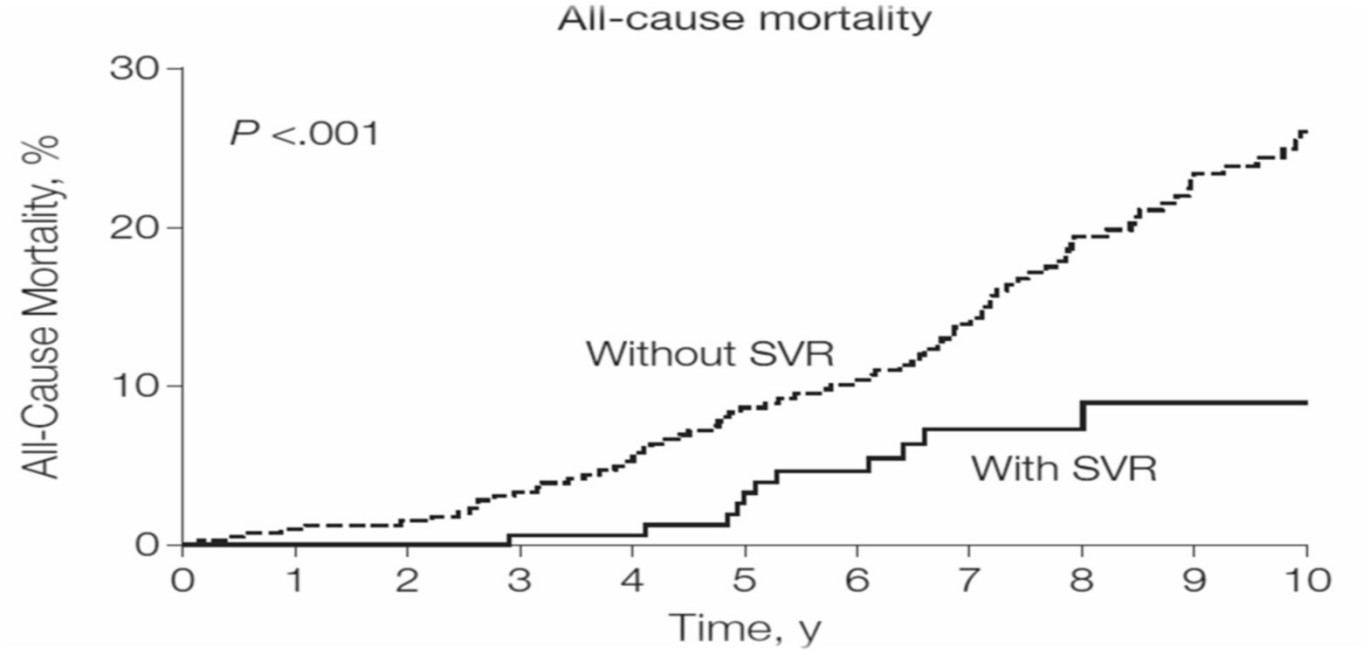
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Wyles, HCVguidelines.org



©2026 Infectious Disease Board Review, LLC

# SVR Reduces Clinical Outcomes




Van der Meer, *JAMA* 2012. Backus, *Clin Gastro* 2011. Imazeki, *Hepatology* 2003. Shiratori, *Ann Intern Med* 2005. Veldt, *Ann Intern Med* 2007. Berenguer, *Hepatology* 2009.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# HCV-HIV ART Drug Interactions

| | | Ledipasvir/ Sofosbuvir (LDV/SOF) | Sofosbuvir/ Velpatasvir (SOF/VEL) | Elbasvir/ Grazoprevir (ELB/GRZ) | Glecaprevir/ Pibrentasvir (GLE/PIB) | Sofosbuvir/ Velpatasvir/ Voxilaprevir (SOF/VEL/VOX) |
|---|---|---|---|---|---|---|
| Protease Inhibitors | Boosted Atazanavir | A | A | | | |
| | Boosted Darunavir | A | A | | | |
| | Boosted Lopinavir | ND, A | A | | | ND |
| NNRTIs | Doravirine | | ND | | ND | ND |
| | Efavirenz | | | | ND | ND |
| | Rilpivirine | | | | | |
| | Etravirine | ND | ND | ND | ND | ND |
| Integrase Inhibitors | Bictegravir | | | ND | ND | |
| | Cabotegravir | ND | ND | ND | ND | ND |
| | Cobicistat-boosted elvitegravir | C | C | | | C |
| | Dolutegravir | | | | | ND |
| | Raltegravir | | | | | ND |
| Entry Inhibitors | Fostemsavir | ND | ND | ND | ND | ND |
| | Ibalizumab-uiyk | ND | ND | ND | ND | ND |
| | Maraviroc | ND | ND | ND | ND | ND |
| NRTIs | Abacavir | | ND | ND | | ND |
| | Emtricitabine | | | | | |
| | Lamivudine | | ND | ND | | ND |
| | Tenofovir disoproxil fumarate | B, C | B, C | | | C |
| | Tenofovir alafenamide | D | D | ND | | D |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

www.hcvguidelines.com



©2026 Infectious Disease Board Review, LLC

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Test, Evaluate, Monitor | Treatment-Naive | Treatment-Experienced | Unique & Key Populations

Recommended regimens listed by evidence level and alphabetically for:

## Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]

| RECOMMENDED | DURATION | RATING |
|---|---|---|
| Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) | 12 weeks | I, A |
| Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] | 8 weeks | I, B |

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Hepatitis B: 2023 Testing Recs for USA

**Universal hepatitis B virus (HBV) screening**

- HBV screening at least once during a lifetime for adults aged ≥18 years (new recommendation)
- During screening, test for hepatitis B surface antigen (HBsAg), antibody to HBsAg, and total antibody to HBcAg (total anti-HBc) (new recommendation)

**Screening pregnant persons**

- HBV screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing*
- Pregnant persons with a history of appropriately timed triple panel screening and without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening) only need HBsAg screening

**Risk-based testing**

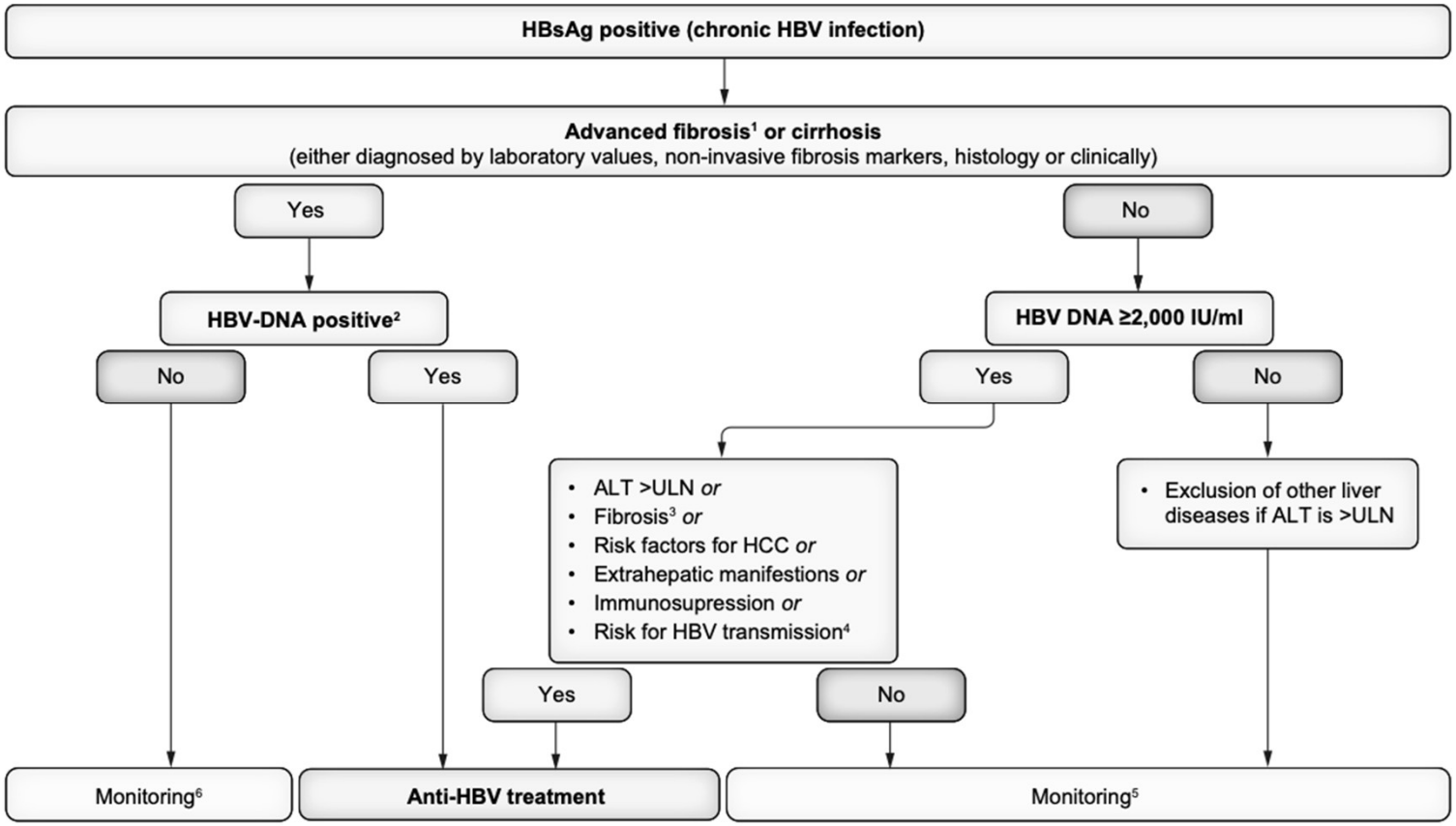
- Testing for all persons with a history of increased risk for HBV infection, regardless of age, if they might have been susceptible during the period of increased risk†
- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposures, while risk for exposures persists†

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

MMWR March 10, 2023



©2026 Infectious Disease Board Review, LLC




EASL J Hepatol 2025; AASLD 2025; WHO 2024

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Phase 3 Results of Bepirovirsen Treatment for Chronic Hepatitis B Virus Infection

**Figure 2. Functional Cure at Week 72 and Key Secondary Outcome, According to Baseline HBsAg Level.**

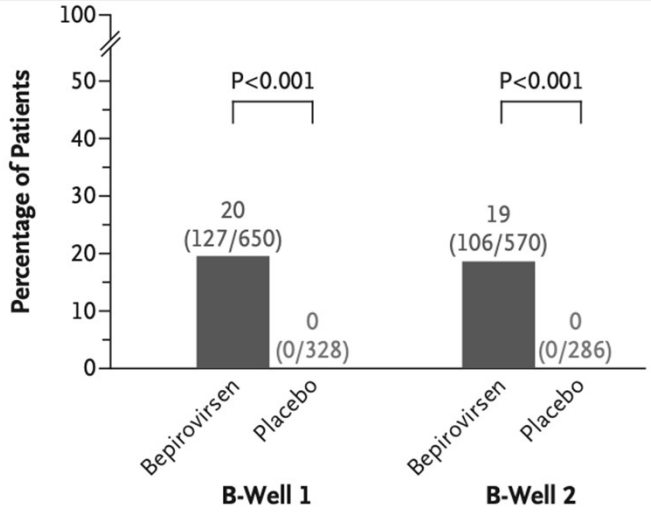
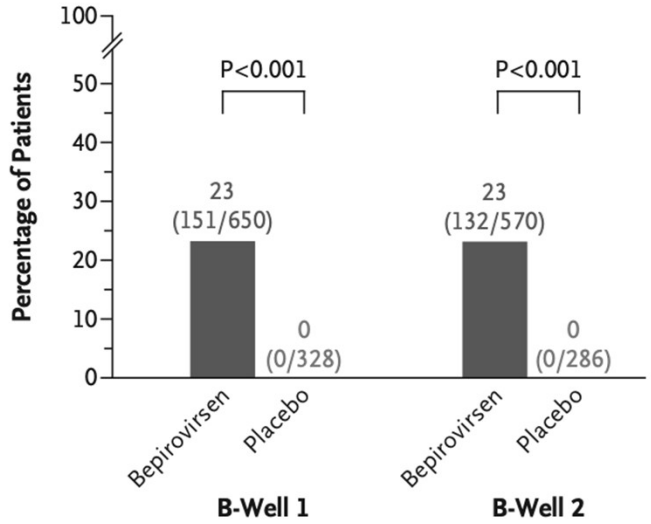



**Figure 3. Discontinuation of NA and HBV DNA below LLOQ or Not Detected at Week 72, According to Baseline HBsAg Level.**




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Hou NEJM 2026



©2026 Infectious Disease Board Review, LLC

# A Phase 3, Randomized Trial of Bulevirtide in Chronic Hepatitis D

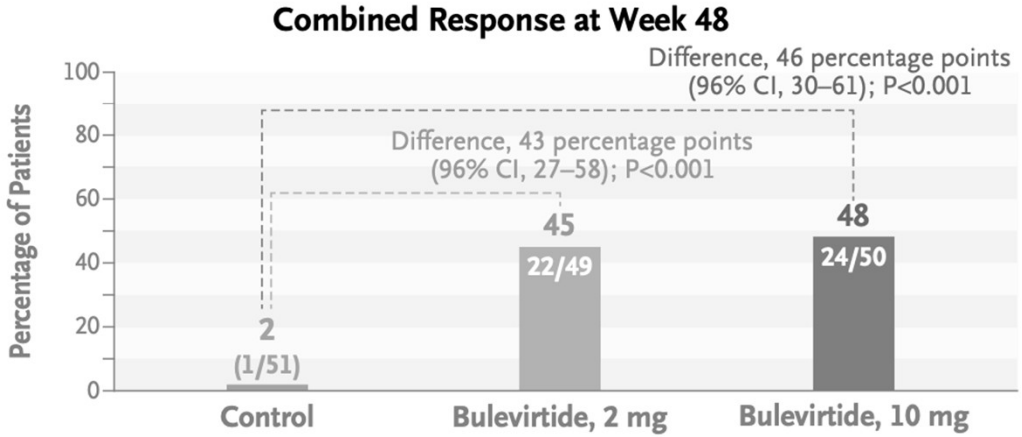
Wedemeyer H. et al. DOI: 10.1058/NJEMoa2213429

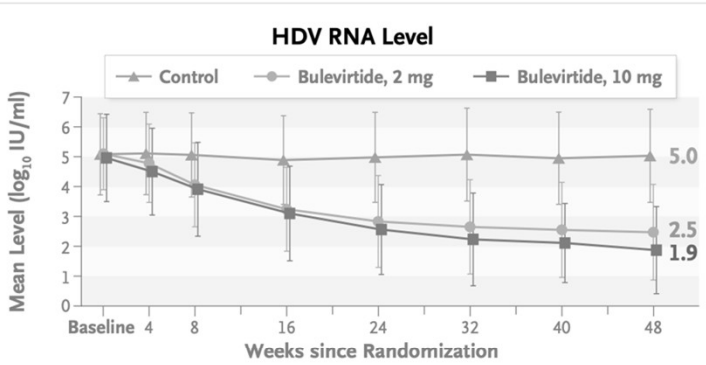
FDA NEWS RELEASE

## FDA Approves First Treatment for Chronic Hepatitis Delta Virus (HDV) Infection

**For Immediate Release:** May 22, 2026

Today, the U.S. Food and Drug Administration approved Hepcludex (bulevirtide-gmod)



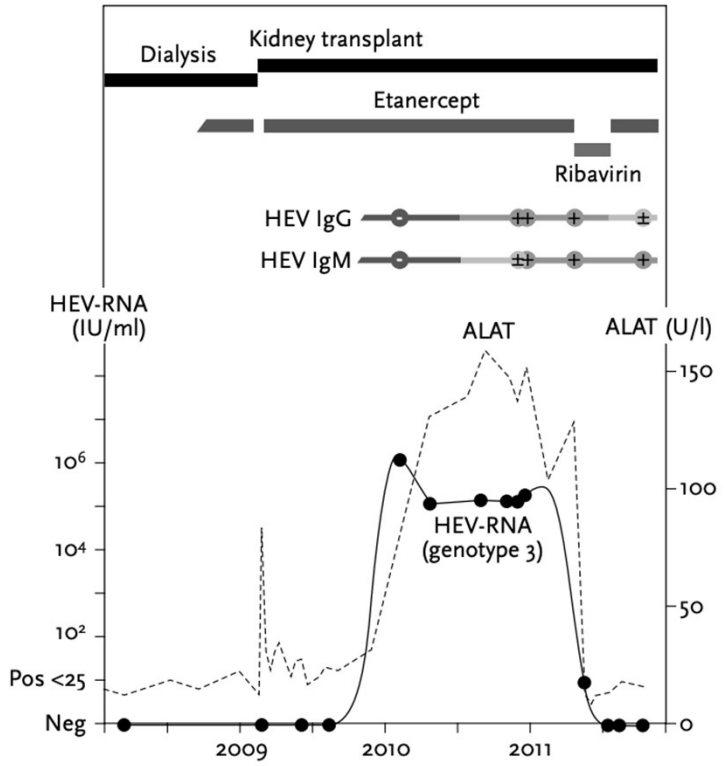

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Chronic HEV in Transplant Recipient

- Europe (boar)
- Can cause cirrhosis
- Tacrolimus associated
- Ribavirin may be effective




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Barrague Medicine 2017



©2026 Infectious Disease Board Review, LLC

Wednesday, August 26, 2026

49

# Nontuberculous Mycobacteria in Normal and Abnormal Hosts

Kevin Winthrop, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# 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**

9/7/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- Research Grant---Insmed, AN2,
- Consultant--- Insmed, AN2

## Nontuberculous Mycobacterium (NTM)

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

## Laboratory Growth Characteristics

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


©2026 Infectious Disease Board Review, LLC

## NTM Disease Clinical Manifestations

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

## 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)

## Other Pearls Based on Species

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

## Question #1

- 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


©2026 Infectious Disease Board Review, LLC

## 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

## Pulmonary NTM

- 2007 ATS/IDSA diagnostic criteria:
- Patient has both radiographic evidence of disease and pulmonary symptoms

  **AND**
- At least 2 sputum cultures positive, or
- One BAL or tissue specimen with positive culture

  **OR**
- Tissue with granulomatous histopathology in conjunction with positive culture (BAL or sputum)

Griffith D et al. *AJRCCM* 2007

## Pulmonary NTM

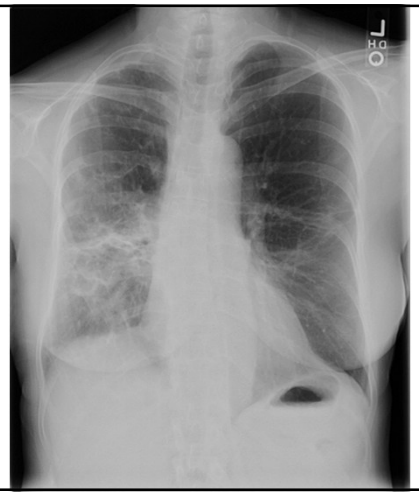
- MAC is most common etiology (60-90%)
- *M. kansasii* and *M. abscessus*
  - *M. kansasii* primarily in the South
  - Recent *M. abscessus* increase in CF
- Other organisms of importance
  - *M. xenopi* (northern US/ Canada, Europe)
  - *M. malmoense* (Europe)

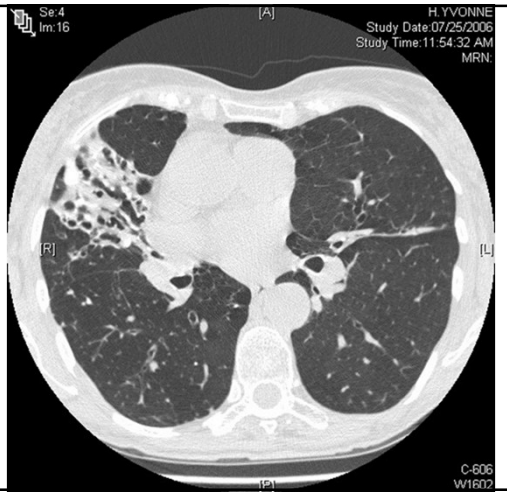
## Two Types of MAC Pulmonary Diseases

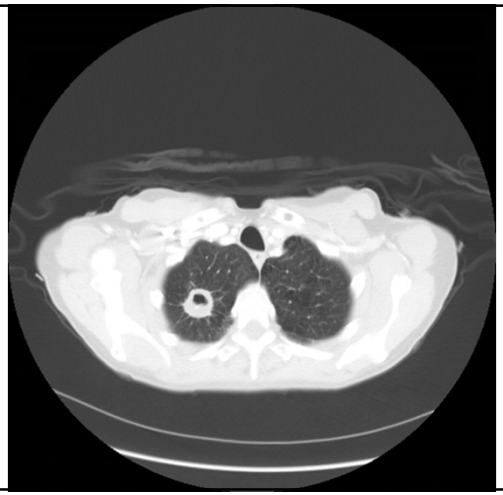
- **Older male, smoker, COPD**
  - Apical cavitary or fibronodular disease
  - More rapidly progressive
- **Older female ("Lady-Windermere")**
  - Scoliosis, thin, pectus deformities*, hypomastia
  - Nodular and interstitial nodular infiltrate
  - Bronchiectasis right middle lobe / lingula
  - Bronchiolitis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

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


©2026 Infectious Disease Board Review, LLC





## 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


©2026 Infectious Disease Board Review, LLC

## NTM Pulmonary Disease Diagnosis

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

## MAC Therapeutic Options

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

## MAC Therapeutic Caveats

- Non-cavitary mild/moderate MAC
  - 2 drugs (AZI/EMB) nearly equivalent to 3 drugs (AZI/EMB/RIF)
  - Encore data show arykace/AZI/EMB is superior to AZI/EMB in treatment naive

## 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


©2026 Infectious Disease Board Review, LLC

## *Pulmonary M. abscessus ssp.* Therapy

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

## *M. abscessus* Therapy

- Parenteral agents
  - Omadacycline 100mg QD, Tigecycline 50mg QD, Cefoxitin 2gm TID, Imipenem 1000mg BID, Amikacin 10mg/kg TIW
- Oral agents
  - Clofazimine 50-100mg QD, Linezolid 600mg QD, moxifloxacin 400mg QD (rarely suscep), Azithromycin 250mg QD (if suscep), Omadacycline 300mg QD
  - Surgical resection

## Extrapulmonary NTM

1. Immunocompetent settings
2. Immunocompromised settings

## Question #2

A 40-year-old construction worker who grew up in central Mexico but is now living in Virginia has had multiple nodules of his left leg between the knee and ankle for at least 3 months.

- His leg is slightly tender and erythematous with nodules but no v fluctuance. There is no inguinal adenopathy.
- He has steroid dependent asthma for which he takes chronic prednisone.
- Otherwise, he feels well, has been working regularly, and has no fever or weight loss.
- He has been to urgent care several times.
- His white blood count and routine chemistries were normal on several occasions. Two weeks courses of doxycycline and cephalexin had no effect.

You obtain a chest x-ray which is normal and CT scan of his leg which shows no fluid collections or bone lesions.

A punch biopsy performed by a dermatologist 4 days ago is growing a mycobacteria


©2026 Infectious Disease Board Review, LLC

## Question #2

**Which Mycobacteria is this most likely to be?**

*A. Mycobacterium gordonae*
*B. Mycobacterium tuberculosis*
*C. Mycobacterium leprae*
*D. Mycobacterium chelonae*
*E. Mycobacterium kansasii*

## Question #2

**Which Mycobacteria is this most likely to be?**

*A. Mycobacterium gordonae*
*B. Mycobacterium tuberculosis*
*C. Mycobacterium leprae*
***D. Mycobacterium chelonae****
*E. Mycobacterium kansasii*

## 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

## 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


©2026 Infectious Disease Board Review, LLC

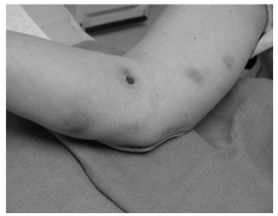
## Post-plastic Surgery



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

## M. Marinum - Fish Tank Granuloma





**Treatment: Multiple Drugs**

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

## Nail Salon Furunculosis

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



## Tattoo-associated

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




©2026 Infectious Disease Board Review, LLC

## Immunosuppression Other than HIV

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

## *M. chelonae* in Cancer Patient



## *M. chelonae* and *M. fortuitum* Treatment

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

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

## *M. chimaera*

- Slow growing. *M. avium* complex
  - Pulmonary disease
- 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 repor
- up to 6 years postoperatively.
- Mycobacterial blood cultures
- Treatment: forever?




©2026 Infectious Disease Board Review, LLC

## Question #3

A 27-year-old male with sickle cell disease presents with a chest syndrome crisis: he has his typical fever, chest pain, and leukocytosis. He is cultured and started on vancomycin and levofloxacin.

His initial chest radiograph shows bilateral infiltrates: an x-ray one week prior showed only some chronic scarring.

- Sputum acid-fast stain negative, and gram stain and culture show normal flora.

- CBC and Chem 12 show a leukocytosis, hemolytic anemia, and mild LFT abnormalities.

Careful physical examination reveals no localizing physical findings: a tunneled double lumen subclavian line, in for 4 months, appears unremarkable.

After 96 hours, the laboratory reports that one blood culture is growing a non-branching beaded Gram-positive bacillus that is acid-fast stain positive.

- Three additional blood cultures are drawn (one through each lumen of the subclavian line) and one peripherally: at 48 hours they are all reported to be positive for an acid-fast non branching rod.

## Question #3

**Which of the following organisms would be most likely?**

A. Nocardia asteroides
B. Mycobacterium mucogenicum
C. Rhodococcus equi
D. Legionella micdadei
E. Mycobacterium tuberculosis

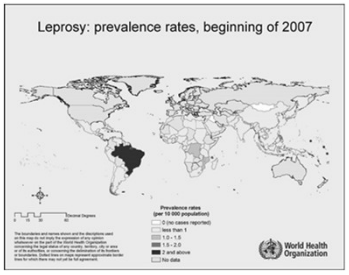
## Question #3

**Which of the following organisms would be most likely?**

A. Nocardia asteroides
**B. Mycobacterium mucogenicum***
C. Rhodococcus equi
D. Legionella micdadei
E. Mycobacterium tuberculosis

## 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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## Leprosy Disease Classification

- Paucibacillary (PB)
  - Most common form
    - "*Tuberculoid*"
    - Bacillary load < 1 million
    - Skin biopsy: AFB negative
    - <5 skin lesions
- Multibacillary (MB)
  - Less common form
  - *"Lepromatous"*
  - Massive bacillary load
  - Skin biopsy: Floridly AFB+
  - >5 skin lesions








©2026 Infectious Disease Board Review, LLC

## Leprosy Treatment

- PB (6-12 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - *Rifampin 600mg once monthly
  - (US recommendations changed in 2025---now once monthly Moxi, RIF, Minocycline, 12-24 months)
- MB (12-24 months)
  - Dapsone 100mg daily
  - Clofazimine 50mg daily
  - Rifampin 600mg daily

Complications: (1) reversal reactions, treat with prednisone/MTX, (2) Erythema nodosum (EN), **treat with thalidomide**, clofaz, apremilast

## Top 10 or 12 NTM Pearls for the Boards

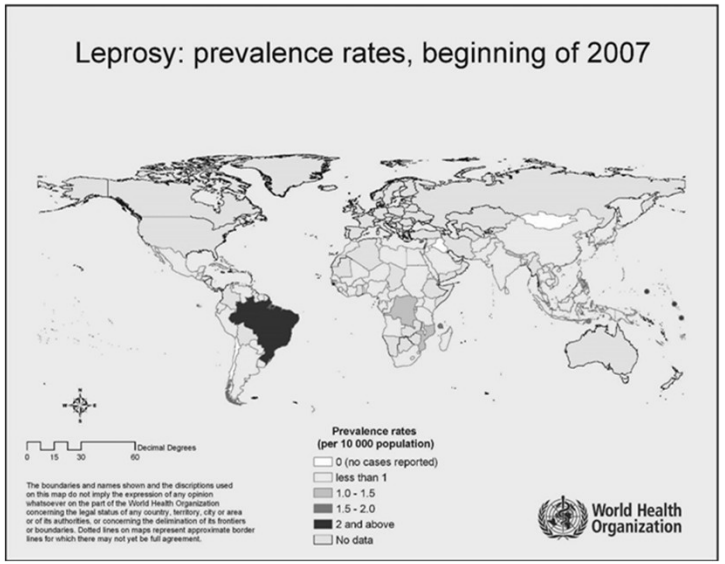
- Footbaths = *M. fortuitum* or other RGM
- Plastic Surgery = *M. chelonae* or other RGM
- Equitorial Africa = *M. ulcerans*
- HIV disseminated MAC that doesn't grow = think of *M. genavense*
- *M. abscessus* usually has inducible macrolide resistance (erm gene)
- Macrolide, EMB, RIF for 18-24 months 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# 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




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

**Wednesday, August 26, 2026**

---

**50**

# Principles of Antimicrobial Therapy for Exam: What You Need to Know About Toxicities, PK/PD, Drug-Drug Interactions

**Douglas Black, Pharm D**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Principles of Antimicrobial Therapy for Exam: PK/PD, Drug-Drug Interactions, and Toxicities

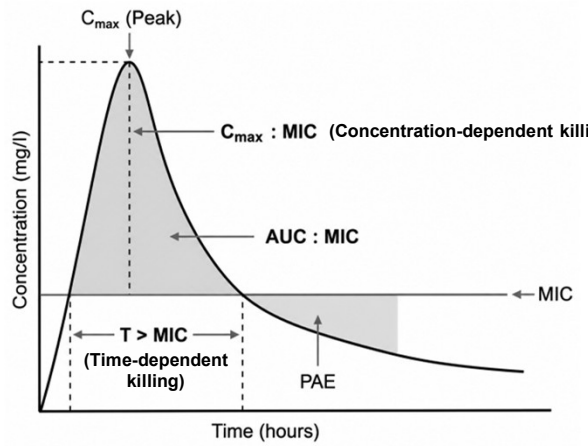
**Douglas Black, Pharm D**
**University of Washington**

9/7/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor, *The Sanford Guide to Antimicrobial Therapy*

| | |
|---|---|
| Pharmacokinetics | Describes the movement of a drug into, through, and out of the body over time. Summarized by ADME: absorption, distribution, metabolism, excretion. |
| Pharmacodynamics | Focuses on the biological and physiological effects of a drug, including its mechanism of action. |
| PK/PD | Establishes and evaluates dose-concentration-response relationships. |




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

## Putting It All Together

| Drugs | Activity | Killing | PAE | PD index |
|---|---|---|---|---|
| β-lactams | Bactericidal | Time-dependent | Minimal* | T>MIC |
| Aminoglycosides<br>Colistin<br>Daptomycin<br>Fluoroquinolones<br>Metronidazole | Bactericidal | Concentration-dependent | Prolonged | Cmax:MIC<br>AUC:MIC |
| Clindamycin<br>Linezolid<br>Macrolides<br>Tetracyclines<br>Tigecycline<br>Vancomycin** | Bacteriostatic | Concentration-dependent | Moderate to prolonged | AUC:MIC |

*Exception: carbapenems (prolonged post-antibiotic effect vs. gram-negative bacilli)
**Vancomycin is bacteriostatic vs enterococci, bactericidal vs staphylococci and streptococci

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**Here are 3 relevant clinical applications of PK/PD principles that you might get asked about…**

- Extended-interval aminoglycoside dosing
- Extended-infusion piperacillin-tazobactam
- Vancomycin AUC monitoring

## PK/PD Question #1

**What is the primary rationale for using extended-interval aminoglycoside dosing instead of conventional dosing?**

A. Therapeutic drug monitoring is no longer necessary
B. The duration of treatment is shortened
C. The need for audiometry is eliminated
D. Clinical cure rates are always improved
E. Nephrotoxicity is generally reduced

## PK/PD Question #1

**What is the primary rationale for using extended-interval aminoglycoside dosing instead of conventional dosing?**

A. Therapeutic drug monitoring is no longer necessary
B. The duration of treatment is shortened
C. The need for audiometry is eliminated
D. Clinical cure rates are always improved
**E. Nephrotoxicity is generally reduced***


©2026 Infectious Disease Board Review, LLC

## Conventional vs. Extended-Interval Aminoglycoside Dosing

| | Aerobic gram-positive infection | Aerobic gram-negative infection |
|---|---|---|
| Conventional | **Preferred** | Use in certain situations* |
| Extended-interval | OK for certain types of streptococcal endocarditis | **Preferred** |

*Burns >20% BSA, cystic fibrosis, age <12 years, ascites, obesity, poor renal function

## PK/PD Question #2

### What is one documented benefit of extended-infusion piperacillin-tazobactam?

A. Less *C. difficile* infection is observed
B. Clinical outcomes are improved in some patients
C. The emergence of resistant isolates is reduced
D. The need for renal dosage adjustment is eliminated
E. CNS penetration of piperacillin is improved

## PK/PD Question #2

### What is one documented benefit of extended-infusion piperacillin-tazobactam?

A. Less *C. difficile* infection is observed
**B. Clinical outcomes are improved in some patients***
C. The emergence of resistant isolates is reduced
D. The need for renal dosage adjustment is eliminated
E. CNS penetration of piperacillin is improved

## Piperacillin-Tazobactam for *Pseudomonas aeruginosa* Infection: Clinical Implications of an Extended-Infusion Dosing Strategy

**Thomas P. Lodise, Jr.,[1,2] Ben Lomaestro,[3] and George L. Drusano[2]**

[1]Department of Pharmacy Practice, Albany College of Pharmacy, [2]Ordway Research Institute, and [3]Department of Pharmacy, Albany Medical Center Hospital, Albany, New York

***Background.*** Piperacillin-tazobactam is frequently used to treat *Pseudomonas aeruginosa* infections in critically ill patients. In an effort to improve clinical outcomes, an extended-infusion dosing scheme for piperacillin-tazobactam therapy was devised using a Monte Carlo simulation and was adopted into clinical practice at Albany Medical Center (Albany, New York). This study evaluates the clinical implications of extended infusion of piperacillin-tazobactam therapy for critically ill patients with *P. aeruginosa* infection.

***Methods.*** We performed a cohort study of patients who received piperacillin-tazobactam therapy for a *P. aeruginosa* infection that was susceptible to piperacillin-tazobactam during the period January 2000–June 2004. Prior to February 2002, all patients received intermittent infusions of piperacillin-tazobactam (3.375 g intravenously for 30 min every 4 or 6 h); after this time, all patients received extended infusions of piperacillin-tazobactam (3.375 g intravenously for 4 h every 8 h). Data on demographic characteristics, disease severity, and microbiology were collected, and outcomes were compared between groups.

***Results.*** A total of 194 patients comprised the 2 study groups: 102 patients received extended infusions of piperacillin-tazobactam, and 92 patients received intermittent infusions of piperacillin-tazobactam. No differences in baseline clinical characteristics were noted between the 2 groups. Among patients with Acute Physiological and Chronic Health Evaluation–II scores ≥17, 14-day mortality rate was significantly lower among patients who received extended-infusion therapy than among patients who received intermittent-infusion therapy (12.2% vs. 31.6%, respectively; $P = .04$), and median duration of hospital stay after collection of samples for culture was significantly shorter for patients who received extended-infusion therapy than for patients who received intermittent-infusion therapy (21 days vs. 38 days; $P = .02$).

***Conclusions.*** These results indicate that extended-infusion piperacillin-tazobactam therapy is a suitable alternative to intermittent-infusion piperacillin-tazobactam therapy, and they strongly suggest that improved outcomes may be realized by administering extended-infusion piperacillin-tazobactam therapy to critically ill patients with *P. aeruginosa* infection.

Clin Infect Dis 2007;44:357-63



©2026 Infectious Disease Board Review, LLC

## PK/PD Question #3

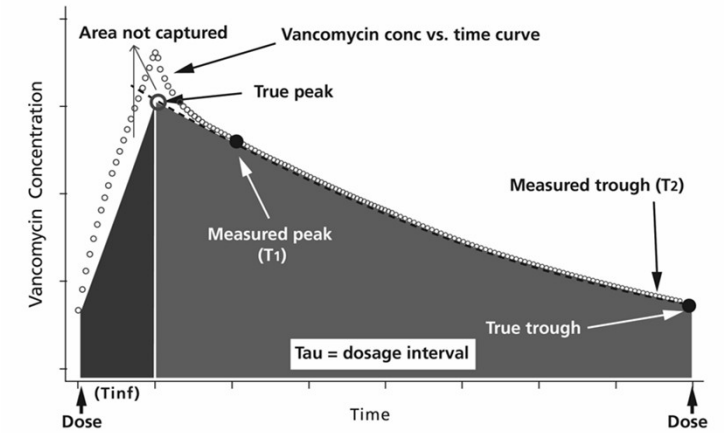
**What is the correct vancomycin AUC to target for treating MRSA pneumonia?**

A. 100-200 µg*hr/mL
B. 200-400 µg*hr/mL
C. 200-600 µg*hr/mL
D. 400-600 µg*hr/mL
E. 400-800 µg*hr/mL

## PK/PD Question #3

**What is the correct vancomycin AUC to target for treating MRSA pneumonia?**

A. 100-200 µg*hr/mL
B. 200-400 µg*hr/mL
C. 200-600 µg*hr/mL
**D. 400-600 µg*hr/mL***
E. 400-800 µg*hr/mL



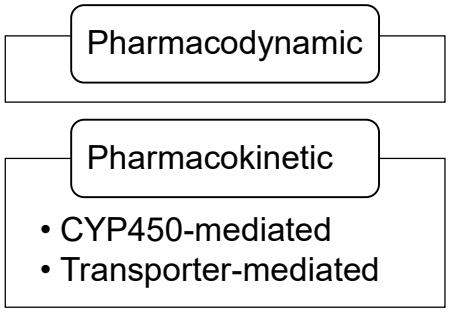

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Vancomycin AUC Monitoring Pearls

- For serious MRSA infections, an AUC of 400-600 should be targeted. MIC is assumed to be 1. This approach will minimize the risk of AKI and maximize efficacy, compared to trough-only monitoring.
- For other pathogens or infections, the routine use of AUC monitoring is not well established and requires further study.
- There are pros and cons to the two methods of determining AUC (trapezoidal equations vs. Bayesian methods).
- If administering vancomycin by continuous infusion, simply multiple steady-state concentration by 24 to calculate $AUC_{24}$.


©2026 Infectious Disease Board Review, LLC

## Moving on to 8 Drug-drug Interactions you Might Get Asked About




## DDI Question #4

- A 72-year-old woman presents to the ED complaining of lightheadedness and a fainting spell
- Increasing fatigue and palpitations over the last 3 days
- Recently diagnosed with an LRI, prescribed clarithromycin 500 mg po bid 4 days ago
- Other problems: atrial fibrillation, hypertension, hyperlipidemia, type 2 diabetes
- Meds: candesartan, amiodarone, metoprolol, atorvastatin, metformin

## DDI Question #4

**A drug-drug interaction between clarithromycin and which drug below best explains this patient's syncopal episode?**

A. Candesartan
B. Amiodarone
C. Metoprolol
D. Atorvastatin
E. Metformin

## DDI Question #4

**A drug-drug interaction between clarithromycin and which drug below best explains this patient's syncopal episode?**

A. Candesartan
**B. Amiodarone***
C. Metoprolol
D. Atorvastatin
E. Metformin


©2026 Infectious Disease Board Review, LLC

## DDI Question #5

- A 67-year-old woman presents to her primary care provider with persistent dysuria and urinary frequency x 5 days
- Started ciprofloxacin 500 mg po bid by urgent care 3 days ago for presumed UTI
- Denies flank pain, fever, hematuria
- PMH: GERD, hypertension, osteoarthritis
- Meds: lisinopril, losartan, omeprazole, sucralfate, acetaminophen

## DDI Question #5

**Administration of which medication should be staggered, if possible, to avoid interacting with ciprofloxacin?**

A. Lisinopril
B. Losartan
C. Omeprazole
D. Sucralfate
E. Acetaminophen

## DDI Question #5

**Administration of which medication should be staggered, if possible, to avoid interacting with ciprofloxacin?**

A. Lisinopril
B. Losartan
C. Omeprazole
**D. Sucralfate***
E. Acetaminophen

## DDI Question #6

- A 75-year-old man started TMP-SMX one DS tablet q12h five days ago for acute prostatitis
- Allergy: levofloxacin (tendon pain)
- He now reports new-onset bruising, bleeding gums, and blood in his stool this morning
- No recent trauma or prior bleeding issues
- Other problems: atrial fibrillation, hypertension, type 2 diabetes
- Meds: warfarin, metformin, amlodipine


©2026 Infectious Disease Board Review, LLC

## DDI Question #6

### What is the most likely explanation for these bleeding symptoms?

A. Inhibition of warfarin metabolism
B. Protein binding displacement
C. Alteration of vitamin-K producing gut flora
D. Myelosuppression from TMP-SMX
E. Changes in the patient's diet

## DDI Question #6

### What is the most likely explanation for these bleeding symptoms?

**A. Inhibition of warfarin metabolism***
B. Protein binding displacement
C. Alteration of vitamin-K producing gut flora
D. Myelosuppression from TMP-SMX
E. Changes in the patient's diet

## DDI Question #7

- A 38-year-old woman has focal epilepsy that is well controlled on phenytoin x3 years
- She presents with new-onset breakthrough seizures
- Two weeks ago, she began treatment for LTBI (rifampin 600 mg daily)
- Serum phenytoin level is 3.2 µg/mL (reference range: 10–20 µg/mL)

## DDI Question #7

### Which of the following best explains the cause of her breakthrough seizures?

A. Rifampin reduces gastrointestinal absorption of phenytoin
B. Rifampin induces hepatic enzymes, lowering phenytoin serum levels
C. Rifampin displaced phenytoin from plasma proteins, increasing clearance
D. Rifampin inhibits P-glycoprotein, reducing phenytoin CNS penetration
E. Rifampin binds directly to phenytoin, inactivating it in the plasma


©2026 Infectious Disease Board Review, LLC

## DDI Question #7

**Which of the following best explains the cause of her breakthrough seizures?**

A. Rifampin reduces gastrointestinal absorption of phenytoin
**B. Rifampin induces hepatic enzymes, lowering phenytoin serum levels***
C. Rifampin displaced phenytoin from plasma proteins, increasing clearance
D. Rifampin inhibits P-glycoprotein, reducing phenytoin CNS penetration
E. Rifampin binds directly to phenytoin, inactivating it in the plasma

## DDI Question #8

- A 42-year-old woman presents with acute agitation, diaphoresis, muscle stiffness, and tremors
- 24 hours ago, she began linezolid 600 mg po q12h for a community-acquired MRSA skin infection
- History of major depressive disorder, takes sertraline 100 mg po q24h
- Other problems: migraine (prn treatment with sumatriptan).
- VS: T 39.2°C, HR 124, BP 159/86, RR 22

## DDI Question #8

**What is the most appropriate initial management?**

A. Discontinue linezolid and sertraline, give IV fluids and benzodiazepines
B. Switch from sertraline to fluoxetine
C. Start cyproheptadine, continue linezolid with dose adjustment
D. Observe without intervention unless seizures occur
E. Continue linezolid and sertraline, add propranolol for symptom control

## DDI Question #8

**What is the most appropriate initial management?**

**A. Discontinue linezolid and sertraline, give IV fluids and benzodiazepines***
B. Switch from sertraline to fluoxetine
C. Start cyproheptadine, continue linezolid with dose adjustment
D. Observe without intervention unless seizures occur
E. Continue linezolid and sertraline, add propranolol for symptom control


©2026 Infectious Disease Board Review, LLC

## DDI Question #9

- A 67-year-old man presents with a 3-day history of increasing muscle pain and weakness in his thighs and calves, and dark colored urine this morning
- Problems: hyperlipidemia, hypertension, onychomycosis (recently diagnosed)
- Meds: simvastatin 40 mg qd (x4 years), metformin 1 gm bid, lisinopril 10 mg qd, itraconazole 200 mg qd (started 6 days ago)
- Labs: CK 12,400 U/L, SCr 1.4 mg/dL (baseline 1.0), mild AST/ALT elevation. UA: myoglobinuria

## DDI Question #9

**Which of the following is a recognized risk factor for statin myopathy in the setting of oral antifungal therapy?**

A. Use of a statin metabolized by CYP1A2
B. Rosuvastatin use
C. Co-administration with metformin
D. Young age
E. Concomitant use of a moderate to strong CYP3A4 inhibitor

## DDI Question #9

**Which of the following is a recognized risk factor for statin myopathy in the setting of oral antifungal therapy?**

A. Use of a statin metabolized by CYP1A2
B. Rosuvastatin use
C. Co-administration with metformin
D. Young age
**E. Concomitant use of a moderate to strong CYP3A4 inhibitor***

## DDI Question #10

- A 72-year-old female complains of progressive weakness, lightheadedness, and occasional palpitations x3 days
- No chest pain or SOB
- Yesterday completed a five-day course of TMP-SMX (1 DS tab bid) for a UTI
- PMH: hypertension, CKD (CrCl ≈ 50), type 2 diabetes
- Meds: losartan 100 mg qd, amlodipine 5 mg qd, metformin 500 mg bid
- Labs: $K^+$ 6.4 mEq/L, SCr 1.5 mg/dL
- ECG: peaked T waves, bradycardia


©2026 Infectious Disease Board Review, LLC

## DDI Question #10

**Which of the following prescribing practices would have been the best way to avoid this situation?**

A. Use nitrofurantoin instead of TMP-SMX
B. Hold the metformin during the course of TMP-SMX
C. Prescribe TMP-SMX at a reduced dose
D. Replaced losartan with lisinopril
E. Discontinue the amlodipine

## DDI Question #10

**Which of the following prescribing practices would have been the best way to avoid this situation?**

**A. Use nitrofurantoin instead of TMP-SMX***
B. Hold the metformin during the course of TMP-SMX
C. Prescribe TMP-SMX at a reduced dose
D. Replaced losartan with lisinopril
E. Discontinue the amlodipine

## DDI Question #11

- A 27-yo woman presents with a severely infected dog bite on her right hand
- You plan to prescribe a course of amoxicillin-clavulanate
- She is taking an oral contraceptive that contains 35 µg of ethinyl estradiol and 0.25 mg of norgestimate
- She asks if she should use condoms while taking the antibiotic

## DDI Question #11

**Which of the following antimicrobial agents is most clearly associated with reducing the efficacy of oral contraceptives?**

A. Amoxicillin-clavulanate
B. Doxycycline
C. Rifampin
D. Azithromycin
E. Ciprofloxacin


©2026 Infectious Disease Board Review, LLC

## DDI Question #11

**Which of the following antimicrobial agents is most clearly associated with reducing the efficacy of oral contraceptives?**

A. Amoxicillin-clavulanate
B. Doxycycline
**C. Rifampin***
D. Azithromycin
E. Ciprofloxacin

## Drug-Drug Interactions
### Key Messages (Questions 1-4)

- Beware of drugs that **prolong the QTc interval**. Both PK and PD interactions can cause problems. Crediblemeds.org is a good website for QT-prolonging drugs.
- When prescribing FQs, always check for **polyvalent cation-containing** medications.
- TMP-SMX increases the bleeding risk from warfarin primarily by **inhibiting its metabolism**. At least four other mechanisms may or may not contribute.
- Rifampin is a **powerful inducer** of most of the major CYP enzymes. It affects many important drug classes, such as antiepileptics. Induction is a slow process.

## Drug-Drug Interactions
### Key Messages (Questions 5-8)

- Linezolid added to an SSRI can cause **serotonin syndrome**, not by affecting the SSRI directly but by inhibiting the enzyme that metabolizes serotonin (monoamine oxidase).
- Always review for CYP450 interactions when prescribing an antimicrobial to someone on a **statin.** Simvastatin and lovastatin are most vulnerable; rosuvastatin or pravastatin are safer.
- Trimethoprim plus an ARB or ACEI can result in **hyperkalemia**, particularly in older patients and those with reduced renal function.
- Rifampin can diminish OC effectiveness, no question. However, available evidence suggests that **non-rifamycin antibiotics do not**, especially if the OC contains at least 30 µg of ethinyl estradiol.

- Enter the drugs in question
  - https://www.drugs.com/drug_interactions.html
  - https://reference.medscape.com/drug-interactionchecker
  - https://www.webmd.com/interaction-checker/default.htm
- The Liverpool sites
  - www.hiv-druginteractions.org
  - www.hep-druginteractions.org
  - www.covid19-druginteractions.org
- *The Sanford Guide to Antimicrobial Therapy*


©2026 Infectious Disease Board Review, LLC

## Finally, 6 Antimicrobial Toxicities You Might Get Asked About

## Toxicity Case #1

- A 72-year-old man with a history of CKD and hypertension is admitted with sepsis secondary to a UTI
- Cefepime 2 gm IV q12h + vancomycin 1 gm IV q12h are begun
- After 5 days of treatment, he begins to exhibit confusion, agitation, and tremors. His family reports that he has become increasingly disoriented and has had difficulty recognizing familiar faces.
- His SCr, previously stable, is found to be elevated

## Cefepime-induced Neurotoxicity (CIN)

- Factors associated with CIN: age, renal function, total dose administered, cefepime trough concentration (>20 µg/mL).
- Mechanism: GABA inhibition.
- Median duration from drug initiation to onset of CIN: 4 days.
- Manifestations: altered mental status, myoclonus, non-convulsive status epilepticus.
- EEG may be helpful, although there are no specific findings.
- Prognosis favorable. Most cases improve within 3 days of drug discontinuation.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

J Antimicrob Chemother 2022;77:2908-2921

## Antimicrobials Associated with Neurotoxicity

- **Beta-lactams** (seizures, encephalopathy)
- **Ethambutol** (optic neuritis, peripheral neuropathy)
- **Fluoroquinolones** (confusion, seizures, peripheral neuropathy, exacerbation of myasthenia gravis)
- **Isoniazid** (peripheral neuropathy, encephalopathy, psychosis, seizures)
- **Linezolid** (peripheral/optic neuropathy, serotonin syndrome)
- **Metronidazole** (peripheral/optic/autonomic neuropathy, encephalopathy)
- **Nitrofurantoin** (peripheral neuropathy)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

## Toxicity Case #2

- A 64-year-old woman presents to the ED with a painful left arm at a previous IV sit
- PMH: atrial fibrillation, type 2 diabetes
- She is diagnosed with superficial thrombophlebitis and sent home. She returns 7 days later with fever and hypotension. Piperacillin-tazobactam + vancomycin are begun.
- BC: positive for MSSA. TTE: no vegetations. She is switched to nafcillin 2 gm IV q4h, planned duration 2 weeks.
- On day 9, routine lab work shows SCr to be 2.1 mg/dL (baseline 0.8), with eosinophilia. A rash on her chest and back is also observed.

## Acute Interstitial Nephritis

- Usually due to drug-induced hypersensitivity. Some infections (HIV, hepatitis) and immune disorders (lupus) have also been implicated
- Typically presents after 2-3 weeks of drug therapy
- Non-oliguric renal dysfunction (↑BUN, ↑Scr) often gets our attention first
- The "classic" triad (fever, rash, eosinophilia) is seen in <33% of patients. Some say the triad includes arthralgia instead of eosinophilia. Patients may complain of flank pain.
- Definitive diagnosis requires kidney biopsy (generally not done)
- Full recovery usually occurs after the offending drug is stopped. Oral steroids have no established role.
- The patient's allergy history should be correctly labeled. Probably drug specific (not class).

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

J Antimicrob Chemother 2022;77:2908-2921

## Drugs Associated with Acute Interstitial Nephritis

- **Beta-lactams** (penicillins, cephalosporins)
- **Rifampin**
- **TMP-SMX**
- **Allopurinol**
- **Immune checkpoint inhibitors**
- **NSAIDs**
- **Proton pump inhibitors**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Toxicity Case #3

- A 45-year-old man with a history of type 2 diabetes and recent diagnosis of MRSA bacteremia started daptomycin therapy 7 days ago.
- He presents with acute onset of dyspnea, dry cough, and fever, which has worsened over the past 24 hours.
- Exam: febrile, tachypneic, and has bilateral crackles on lung auscultation.
- Chest X-ray shows bilateral infiltrates consistent with pneumonia.
- Lab: elevated eosinophil count.



©2026 Infectious Disease Board Review, LLC

## Daptomycin-induced Eosinophilic Pneumonia (DIEP)

- Rare but potentially severe
- Pathogenesis unestablished
- Unclear if DIEP is dose-related
- Onset typically 2-4 weeks
- Clinical features: new-onset fever, progressive dyspnea, cough (usually non-productive), diffuse bilateral pulmonary infiltrates, hypoxemia
- Also observed: peripheral eosinophilia, elevated inflammatory markers (ESR, CRP)
- BAL: >25% eosinophils, or eosinophilic pneumonia at lung biopsy
- Clinical improvement after discontinuation of daptomycin, corticosteroid administration

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Toxicity Case #4

- A 44-yo woman with AML undergoes allogeneic HSCT
- Course is complicated by severe GVHD with liver and intestinal involvement, treated with high-dose corticosteroids and infliximab
- Develops disseminated *Scedosporium apiospermum* infection with multiorgan involvement
- Treated with IV voriconazole, then oral voriconazole adjusted to maintain a trough concentration of 1.5-5 µg/mL
- 9 months after starting therapy, she complains of severe, disabling bone pain, arthralgias, and swelling of her hands and fingers

## Voriconazole-associated Periostitis

- Prevalence not known
- Features: generalized bone pain, ↑alkaline phosphatase, evidence of periostitis and/or exostoses on x-ray
- Any bones can be affected, but the most common are ribs, forearms, legs, and shoulders
- Takes a long time to occur, at least six weeks but often much longer
- Cause: excess fluoride exposure
- Related to voriconazole dose
- CYP2C19 ultrarapid metabolizers may have increased generation of free fluoride (as well the need for a high voriconazole dose)
- Resolves within 2 months of drug discontinuation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Toxicity Case #5

- A 78-year-old woman being treated for UTI presents with recent symptoms of dyspnea, fatigue, and productive cough
- VS normal, no rash
- PMH: history of recurrent *E. coli* UTI, including an episode 4 months ago (treated with nitrofurantoin)
- Non-smoker
- Started another course of nitrofurantoin 3 days ago (100 mg bid x5 days)
- Chest X-ray: bilateral interstitial infiltrates, patchy ground-glass opacities, pleural effusion
- Lab: WBC 13,500/µL, eosinophils 10%. Other labs WNL.


©2026 Infectious Disease Board Review, LLC

## Acute Nitrofurantoin Pulmonary Toxicity

- Occurs in about 1 in 5000 patients
- Typically presents about 9 days after a short course of therapy in women, age 60-70. Onset is shorter in repeat exposures.
- Think of as a hypersensitivity reaction (type I or III)
- Common symptoms: fever, dyspnea, cough, rash
- PE: inspiratory crackles
- Lab: eosinophilia, leukocytosis, elevated ESR
- Imaging: Diffuse parenchymal changes, pleural effusions
- Treatment: stop drug, document as allergy, avoid re-exposure. Steroids of unproven benefit.
- Improvement within 24-48 hours, full recovery in a few weeks

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Chronic Nitrofurantoin Pulmonary Toxicity

- Develops after several months or years of long-term therapy (women, age 60-70)
- A cell-mediated or toxic response, possibly to drug metabolites
- Common symptoms: Dyspnea, dry cough, fatigue. Fever uncommon. Overall, symptoms less intense than in an acute reaction.
- PE: dry crackles
- Lab: elevated serum gamma globulins, eosinophilia, elevated transaminases, elevated ESR. Maybe ANA+
- Imaging: Parenchymal opacities. Ground glass opacities on CT. Pleural effusion uncommon.
- Higher risk of parenchymal injury
- Treatment: stop drug. Steroids of unproven benefit. Clinical improvement in weeks to months, may not fully resolve.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Toxicity Case #6

- A 68-yo female presents with complaints of dizziness and palpitations
- PMH: hypertension, type 2 diabetes
- One week ago, prescribed levofloxacin 500 mg po q24h for CAP
- VS stable, physical exam unremarkable
- ECG: QTc 520 ms. Baseline (6 months earlier) is 430 ms
- Lab: electrolytes WNL. Troponins negative, echo shows normal LV function

## FQ-induced QTc Interval Prolongation

- Increases risk of serious ventricular arrhythmias (e.g., torsade de pointes)
- Mechanism: blockade of potassium channels
- Risk factors
  - Older age
  - Female
  - Congenital long QT syndrome
  - Bradycardia
  - CHF
  - Hypokalemia, hypomagnesemia
  - Other QT-prolonging drugs
- Symptoms: palpitations, lightheadedness or dizziness, fatigue, syncope
- Likelihood: moxifloxacin > levofloxacin > ciprofloxacin
- Consider ECG monitoring in high-risk patients

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## Antimicrobial Classes Associated with QTc-interval Prolongation

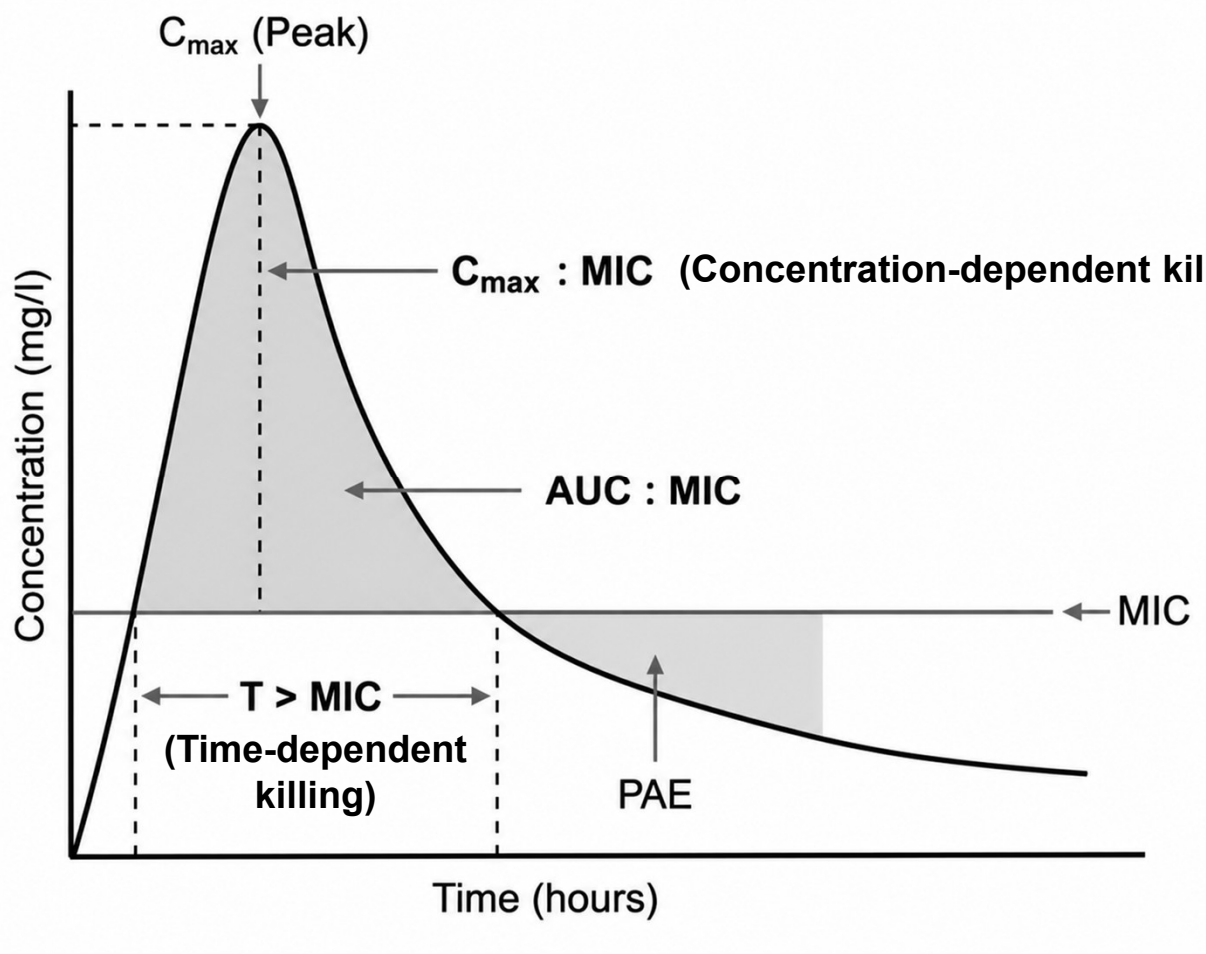
- **Anti-parasitics:** antimony, antimalarials, fexinidazole
- **ARVs:** atazanavir, efavirenz, rilpivirine
- **Azole antifungals**
- **Fluoroquinolones**
- **Macrolides**
- **Other antibacterials:** gepotidacin, lefamulin
- **Pentamidine**
- Good Internet source: crediblemeds.org

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION





©2026 Infectious Disease Board Review, LLC




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

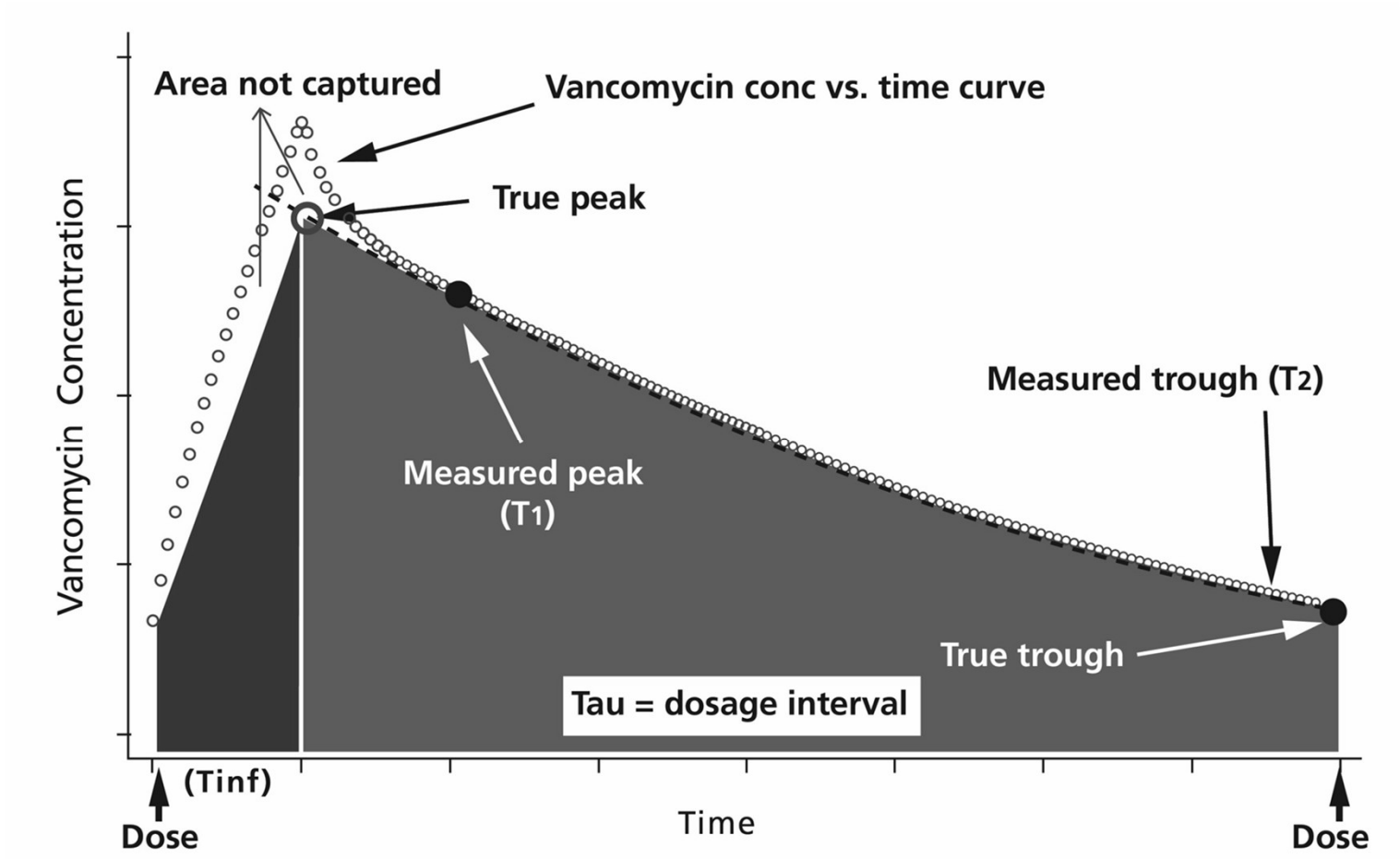
# Putting It All Together

| Drugs | Activity | Killing | PAE | PD index |
|---|---|---|---|---|
| β-lactams | Bactericidal | Time-dependent | Minimal* | T>MIC |
| Aminoglycosides<br>Colistin<br>Daptomycin<br>Fluoroquinolones<br>Metronidazole | Bactericidal | Concentration-dependent | Prolonged | Cmax:MIC<br>AUC:MIC |
| Clindamycin<br>Linezolid<br>Macrolides<br>Tetracyclines<br>Tigecycline<br>Vancomycin** | Bacteriostatic | Concentration-dependent | Moderate to prolonged | AUC:MIC |

*Exception: carbapenems (prolonged post-antibiotic effect vs. gram-negative bacilli)
**Vancomycin is bacteriostatic vs enterococci, bactericidal vs staphylococci and streptococci

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Cefepime-induced Neurotoxicity (CIN)

- Factors associated with CIN: age, renal function, total dose administered, cefepime trough concentration (>20 µg/mL).
- Mechanism: GABA inhibition.
- Median duration from drug initiation to onset of CIN: 4 days.
- Manifestations: altered mental status, myoclonus, non-convulsive status epilepticus.
- EEG may be helpful, although there are no specific findings.
- Prognosis favorable. Most cases improve within 3 days of drug discontinuation.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

J Antimicrob Chemother 2022;77:2908-2921



©2026 Infectious Disease Board Review, LLC

# Antimicrobials Associated with Neurotoxicity

- **Beta-lactams** (seizures, encephalopathy)
- **Ethambutol** (optic neuritis, peripheral neuropathy)
- **Fluoroquinolones** (confusion, seizures, peripheral neuropathy, exacerbation of myasthenia gravis)
- **Isoniazid** (peripheral neuropathy, encephalopathy, psychosis, seizures)
- **Linezolid** (peripheral/optic neuropathy, serotonin syndrome)
- **Metronidazole** (peripheral/optic/autonomic neuropathy, encephalopathy)
- **Nitrofurantoin** (peripheral neuropathy)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Acute Interstitial Nephritis

- Usually due to drug-induced hypersensitivity. Some infections (HIV, hepatitis) and immune disorders (lupus) have also been implicated
- Typically presents after 2-3 weeks of drug therapy
- Non-oliguric renal dysfunction (↑BUN, ↑Scr) often gets our attention first
- The “classic” triad (fever, rash, eosinophilia) is seen in <33% of patients. Some say the triad includes arthralgia instead of eosinophilia. Patients may complain of flank pain.
- Definitive diagnosis requires kidney biopsy (generally not done)
- Full recovery usually occurs after the offending drug is stopped. Oral steroids have no established role.
- The patient's allergy history should be correctly labeled. Probably drug specific (not class).

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

J Antimicrob Chemother 2022;77:2908-2921



©2026 Infectious Disease Board Review, LLC

# Drugs Associated with Acute Interstitial Nephritis

- **Beta-lactams** (penicillins, cephalosporins)
- **Rifampin**
- **TMP-SMX**
- **Allopurinol**
- **Immune checkpoint inhibitors**
- **NSAIDs**
- **Proton pump inhibitors**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Daptomycin-induced Eosinophilic Pneumonia (DIEP)

- Rare but potentially severe
- Pathogenesis unestablished
- Unclear if DIEP is dose-related
- Onset typically 2-4 weeks
- Clinical features: new-onset fever, progressive dyspnea, cough (usually non-productive), diffuse bilateral pulmonary infiltrates, hypoxemia
- Also observed: peripheral eosinophilia, elevated inflammatory markers (ESR, CRP)
- BAL: >25% eosinophils, or eosinophilic pneumonia at lung biopsy
- Clinical improvement after discontinuation of daptomycin, corticosteroid administration

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Voriconazole-associated Periostitis

- Prevalence not known
- Features: generalized bone pain, ↑alkaline phosphatase, evidence of periostitis and/or exostoses on x-ray
- Any bones can be affected, but the most common are ribs, forearms, legs, and shoulders
- Takes a long time to occur, at least six weeks but often much longer
- Cause: excess fluoride exposure
- Related to voriconazole dose
- CYP2C19 ultrarapid metabolizers may have increased generation of free fluoride (as well the need for a high voriconazole dose)
- Resolves within 2 months of drug discontinuation

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Acute Nitrofurantoin Pulmonary Toxicity

- Occurs in about 1 in 5000 patients
- Typically presents about 9 days after a short course of therapy in women, age 60-70. Onset is shorter in repeat exposures.
- Think of as a hypersensitivity reaction (type I or III)
- Common symptoms: fever, dyspnea, cough, rash
- PE: inspiratory crackles
- Lab: eosinophilia, leukocytosis, elevated ESR
- Imaging: Diffuse parenchymal changes, pleural effusions
- Treatment: stop drug, document as allergy, avoid re-exposure. Steroids of unproven benefit.
- Improvement within 24-48 hours, full recovery in a few weeks

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Chronic Nitrofurantoin Pulmonary Toxicity

- Develops after several months or years of long-term therapy (women, age 60-70)
- A cell-mediated or toxic response, possibly to drug metabolites
- Common symptoms: Dyspnea, dry cough, fatigue. Fever uncommon. Overall, symptoms less intense than in an acute reaction.
- PE: dry crackles
- Lab: elevated serum gamma globulins, eosinophilia, elevated transaminases, elevated ESR. Maybe ANA+
- Imaging: Parenchymal opacities. Ground glass opacities on CT. Pleural effusion uncommon.
- Higher risk of parenchymal injury
- Treatment: stop drug. Steroids of unproven benefit. Clinical improvement in weeks to months, may not fully resolve.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# FQ-induced QTc Interval Prolongation

- Increases risk of serious ventricular arrhythmias (e.g., torsade de pointes)
- Mechanism: blockade of potassium channels
- Risk factors
  - Older age
  - Female
  - Congenital long QT syndrome
  - Bradycardia
  - CHF
  - Hypokalemia, hypomagnesemia
  - Other QT-prolonging drugs
- Symptoms: palpitations, lightheadedness or dizziness, fatigue, syncope
- Likelihood: moxifloxacin > levofloxacin > ciprofloxacin
- Consider ECG monitoring in high-risk patients

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Antimicrobial Classes Associated with QTc-interval Prolongation

- **Anti-parasitics:** antimony, antimalarials, fexinidazole
- **ARVs:** atazanavir, efavirenz, rilpivirine
- **Azole antifungals**
- **Fluoroquinolones**
- **Macrolides**
- **Other antibacterials:** gepotidacin, lefamulin
- **Pentamidine**
- Good Internet source: crediblemeds.org

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

**Wednesday, August 26, 2026**

---

**51**

# Infections of Upper and Lower Urinary Tract

**Barbara Trautner, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Infections of Upper and Lower Urinary Tract

**Barbara Trautner, MD**
**Washington University School of Medicine**

9/7/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Topics to Cover

- Acute cystitis in women
- Recurrent cystitis in women
- Asymptomatic bacteriuria
- Catheter-associated UTI
- Complicated UTI
- Pyelonephritis
- Urosepsis and worse




## UTI Differs in Different Populations

UTI is not the same entity in these different populations





©2026 Infectious Disease Board Review, LLC

## The Great Divide in UTI Knowledge (Cystitis)

**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

IDSA ID Topics Practice Resources Education & Training Policy & Advocacy

View All Guidelines

IDSA PRACTICE GUIDELINES CURRENT

Complicated Urinary Tract Infections (cUTI): Clinical Guidelines for Treatment and Management

**Published** July 17, 2025

## New classifications of uUTI and cUTI

| Old Classifications | New Classifications |
|---|---|
| **Uncomplicated UTI:** Acute cystitis in afebrile nonpregnant premenopausal women with no diabetes and no urologic abnormalities | **Uncomplicated UTI: Infection confined to the bladder** in afebrile women or men |
| **Acute Pyelonephritis:** Acute kidney infection in women otherwise meeting the definition of uncomplicated UTI above | **Complicated UTI: infection beyond the bladder** in women or men<br>• Pyelonephritis<br>• Febrile or bacteremic UTI<br>• Catheter-associated (CAUTI)<br>• Prostatitis* (*not covered by these guidelines) |
| **Complicated UTI:** All other UTIs | |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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


©2026 Infectious Disease Board Review, LLC

## 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?**

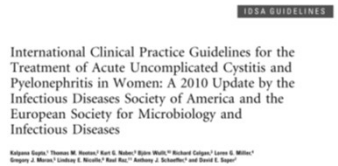
**A. Nitrofurantoin* (Best choice for uncomplicated cystitis when TMP/SMX not an option)**
B. TMP/SMX
C. Fosfomycin
D. Ciprofloxacin
E. Ibuprofen

HPF: high-powered field; TMP/SMX: trimethoprim/sulfamethoxazole

## Infectious Diseases Society of America (IDSA) Uncomplicated UTI Guidelines*

*Complicated UTI guidelines released July 2025

- These guidelines cover:
- Uncomplicated cystitis
- Uncomplicated pyelonephritis
- Premenopausal women
- Primarily outpatients

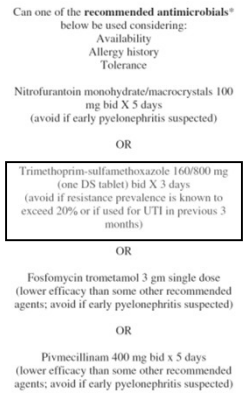

IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

## IDSA Cystitis Guidelines (2010)

**First-line Agents**
- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin
- Pivmecillinam

**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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

BID: twice daily; DS: double strength

## How Long do you Treat Acute Cystitis?

**First line choices (5, 3, 1)**
- Nitrofurantoin X 5
- Pivmecillinam X 5
- Trimethoprim/sulfamethoxazole X 3
- Fosfomycin X1

IDSA Guidelines on Uncomplicated Cystitis, 2010


©2026 Infectious Disease Board Review, LLC

## Antibiotics for Cystitis: Key Points

- Nitrofurantoin
  - High barrier to resistance in *E. coli*
  - Pulmonary toxicity (rare), hepatic toxicity (very rare)
- Pivmecillinam
  - TID dosing
  - Very expensive in US
- Trimethoprim/sulfamethoxazole
  - Significant resistance particularly among E. coli
  - Watch out for hyperkalemia, mild creatinine elevation, rashes
- Fosfomycin
  - Expensive in US
  - Sensitivity testing not automated

## New Antibiotics for UTI with FDA Approval

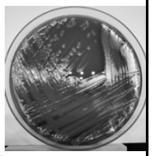
**Uncomplicated UTI**
- Pivmecillinam
- Gepotidacin
- Sulopenem etzadroxil/probenecid

**Complicated UTI**
- Tebipenem pivoxil
- Fosfomycin disodium (IV)
- Cefepime/zidebactam

**Barriers to use**:
Cost, lack of susceptibility testing, availability

## New Oral Drugs for Cystitis: FDA Approved for Uncomplicated UTI

- Pivmecillinam (Pivya)
  - Pro-drug of mecillinam
  - Binds to PBP-2 in Gram-negative cell wall
  - Effective against ESBL+ Enterobacterales, Staph saprophyticus
- Gepotidacin (Blujepa)
  - Blocks DNA topoisomerase
  - Effective against ESBL+ Enterobacterales, S. saprophyticus, and E. faecalis
  - Does not get into the prostate or kidneys
  - Also approved for gonorrhea
- Sulopenem etzadroxil/probenecid (Orlynvah)
  - Thiopenem—new beta-lactam class
  - Effective against ESBL+ Enterobacterales, S. saprophyticus
  - Did not get approval for complicated UTI



Not for *Pseudomonas* or VRE

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## 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


©2026 Infectious Disease Board Review, LLC

## 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

## Question #2 - Rationale

- 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 - 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

## 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 before or 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 (2025)
https://www.auanet.org/guidelines-and-quality/guidelines/recurrent-uti

## Non-antibiotic Strategies to Prevent Recurrent UTI

**Likely Helpful (FDA Approved)**

- Increasing fluid intake
- Vaginal estrogen in post-menopausal women
- Methenamine hippurate

**Uncertain Benefit (Not FDA Approved)**

- Other behavioral changes
- Cranberry products
- D-mannose
- Probiotics
- Other supplements

Fluid intake: Hooton TM, et al. *JAMA Intern Med*. 2018
Methenamine trials: Harding C, et al. ALTAR trial, *Health Technol Assess*. 2022
Botros C, et al. *Int Urogynecol J*. 2022; Heltveit-Olsen ImpresU trial, Clin Microbiol Infect 2025
Systematic review of cranberry products: Williams G, et al. *Cochrane Database Syst Rev*. 2023


©2026 Infectious Disease Board Review, LLC

## 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 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

## 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 vital signs and other physical examination findings are normal.
- On dipstick urinalysis, urine is yellow and with a bad smell, specific gravity is 1.010, pH is 7.0, and moderate leukocyte esterase and nitrites are present; the urinalysis is negative for blood or glucose but 2+ for bacteria.

**Which of the following is the most appropriate management?**

A. Nitrofurantoin
B. Ciprofloxacin
C. Cystoscopy
D. Urine culture and sensitivities
**E. No further infectious workup***

## Prevalence of Asymptomatic Bacteriuria

| Population | Prevalence, % |
|---|---|
| Children | |
| Boys | <1 |
| Girls | 1–2 |
| Healthy women | |
| Premenopausal | 1.0–5.0 |
| 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Mo: month; y: year

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019

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.


©2026 Infectious Disease Board Review, LLC

## 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**

- Infants and children
- Non-pregnant women
- Functionally-impaired older adults
- Diabetic adults
- Patients >1 month from kidney transplant
- Neutropenic patients
- Patients with solid organ transplant
- Persons with spinal cord injury
- Patients with indwelling catheters
- Prior to non-urologic surgery

## 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Warning: Myth-busting Ahead!



## Myth-Busting

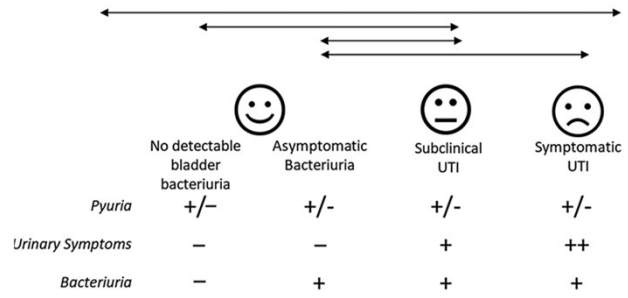
- Bacteriuria ≠ UTI
- Pyuria ≠ UTI
  - WBC in the urine doesn't help much with diagnosis of UTI
  - Absence of pyuria suggests to look for a non-UTI diagnosis
- Foul smelling urine ≠ UTI
- Sediment or cloudy urine in catheter tubing ≠ UTI
  - Try flushing the catheter
- Healthy bladders are not sterile 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

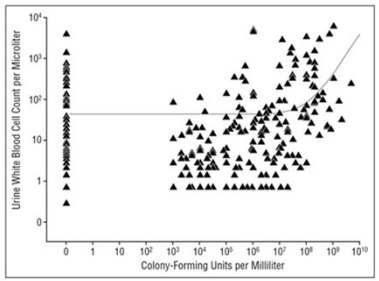

©2026 Infectious Disease Board Review, LLC

# The Continuum of UTI




Trautner, Clin Infect Dis, 2020

# Relationship Between Pyuria and Bacteriuria/Candiduria in Catheterized Patients




CFU: colony-forming unit

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 $10^8$

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Tambyah and Maki, Arch Intern Med. 2000 Mar 13;160(5):678-82 and 673-7

# 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

# 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* - 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


©2026 Infectious Disease Board Review, LLC

## 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

## 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

## Question #5 - Rationale

- 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 kidneys *
E. Use of antiseptic-coated urinary catheters
   - Minimal impact and approved only for short-term use



## Question #6

- An 80-year-old man with T12 paraplegia and an indwelling Foley presents with suspected complicated UTI. He has a temp of 100.1 F and rigors. SOFA score 2, responds to fluid resuscitation (sepsis, without shock). In the prior 12 months his urine cultures showed E. coli and Klebsiella resistant to TMP/SMX, cefazolin, and ceftriaxone. No fluoroquinolone exposure within the past year. No allergies to any antibiotics.

**Assuming that the antibiogram shows greater than 80% susceptibility to all of the following antibiotics, which are the best options?**

A. Levofloxacin
B. Ertapenem
C. Ceftazidime-avibactam
D. Gentamicin
E. A or B


©2026 Infectious Disease Board Review, LLC

## Question #6

- An 80-year-old man with T12 paraplegia and an indwelling Foley presents with suspected complicated UTI. He has a temp of 100.1 F and rigors. SOFA score 2, responds to fluid resuscitation (sepsis, without shock). In the prior 12 months his urine cultures showed E. coli and Klebsiella resistant to TMP/SMX, cefazolin, and ceftriaxone. No fluoroquinolone exposure within the past year. No allergies to any antibiotics.

**Assuming that the antibiogram shows greater than 80% susceptibility to all of the following antibiotics, which are the best options?**

A. Levofloxacin
B. Ertapenem
C. Ceftazidime-avibactam
D. Gentamicin
**E. A or B***

## IDSA cUTI Guideline in a Nutshell

IDSA

- New classification of cUTI
  - Includes febrile UTI, pyelonephritis, CAUTI, bacteremic UTI
- Selection of empiric antibiotic therapy for cUTI
  - **Four-step process**: Review (1) severity of illness, (2) risk factors for resistant organisms, (3) patient factors, and (4) antibiogram (only if septic)
  - **Preferred agents (select from remaining options AFTER completing steps above)**: third- or fourth-generation cephalosporins, carbapenems (if septic), piperacillin-tazobactam, or fluoroquinolones
- Route of antibiotic therapy
  - Oral switch recommended versus continuing IV
- Duration of antibiotic therapy
  - 7 days recommended versus longer courses



IDWeek

## Choice of Empiric Agent for cUTI

IDSA

| Condition of the Patient | Preferred | Alternative |
|---|---|---|
| **Sepsis** with or without shock | Third or fourth generation cephalosporins, carbapenems, piperacillin-tazobactam, fluoroquinolones | Novel beta lactam-beta lactamase inhibitors, cefiderocol, plazomicin, or older aminoglycosides |
| **Without sepsis, IV** route of therapy | Third or fourth generation cephalosporins, piperacillin-tazobactam, or fluoroquinolones | Carbapenems, newer agents (novel beta lactams-beta lactamase inhibitors, cefiderocol, plazomicin), or older aminoglycosides |
| **Without sepsis, oral** route of therapy | Fluoroquinolones or trimethoprim-sulfamethoxazole | Amoxicillin-clavulanate or oral cephalosporins |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## IDSA treatment approach

IDSA

**Step 1**
- **Consider severity of illness:**
  - Sepsis with shock, sepsis without shock, no sepsis

**Step 2**
- **Evaluate patient-specific risk factors for resistant organisms:**
  - Avoid antibiotics to which patient has had resistant pathogen previously isolated
  - Avoid fluoroquinolones (FQ) if patient exposed to FQ in past 12 months

**Step 3**
- **Assess other patient-specific factors:**
  - Risk of allergic reaction, contraindications, drug–drug interactions

**Step 4**
- **If septic use antibiogram to tailor empiric therapy:**
  - Consider at least 90% susceptibility threshold for sepsis with shock
  - Consider at least 80% susceptibility threshold for sepsis without shock
  - Patients not septic have lower (<5%) risk of mortality and initial inappropriate empiric choice has little impact on mortality

IDWeek

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## Let's apply the 4 steps to our patient:

- 80-year-old man with ASIA A paraplegia below T12
- Neurogenic bladder with chronic indwelling Foley
- Temp of 100.1F with rigors
- SOFA score = 2 (STEP 1)
  - No pressors needed (sepsis, without shock)
- Urine cultures within past 12 months (STEP 2)
  - *E. coli* and *Klebsiella* resistant to TMP/SMX, cefazolin, and ceftriaxone
- No fluoroquinolone exposure within the past year (STEP 2)
- No allergies or contraindications to any antibiotics (STEP 3)

IDWeek

## Applying the Antibiogram (Step 4)

| Susceptibilities: | Levofloxacin | Ceftriaxone | Ertapenem | Ceftazidime-Avibactam | Amikacin |
|---|---|---|---|---|---|
| *E. coli* | 82% | 85% | 90% | 95% | 99% |

- Consider the source of the antibiogram isolates (#, timing, setting)
- For sepsis without shock, the target is at least 80% susceptibility
- Best choices for this patient with sepsis, no shock
  - **A. Levofloxacin**
  - **B. Ertapenem**
  - C. Ceftazidime-avibactam—less preferred due to stewardship issues
  - D. Gentamicin—less preferred due to renal toxicity
  - **E. A or B**

Urine grew ESBL+ *E. coli*, treated with ciprofloxacin

IDWeek

## Question #7

- 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 (TMP/SMX)
B. Oral ciprofloxacin
C. One dose of ceftriaxone or gentamicin followed by oral ciprofloxacin or TMP/SMX
D. Oral fosfomycin
E. Nitrofurantoin

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

## Question #7

- 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 (TMP/SMX)
B. Oral ciprofloxacin
**C. One dose of ceftriaxone or gentamicin followed by oral ciprofloxacin or TMP/SMX***
D. Oral fosfomycin
E. Nitrofurantoin

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate


©2026 Infectious Disease Board Review, LLC

## Question #7: Rationale

- 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 (TMP/SMX)
B. Oral ciprofloxacin
**C. One dose of ceftriaxone or gentamicin followed by oral ciprofloxacin or TMP/SMX* - saftest empiric options without cultures to guide you and with known prior antibiotic exposure**
D. Oral fosfomycin - unclear role in pyelonephritis as initial therapy
E. Nitrofurantoin - not effective tissue levels

BP, blood pressure; HR, heart rate; IM, intramuscular; RR, respiratory rate

## Management of Pyelonephritis

- Many clinical trials included pyelonephritis with complicated UTI
- Complicated UTI 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, fosfomycin, piperacillin-tazobactam, carbapenems, fluoroquinolones
- To avoid: nitrofurantoin
- Role of fosfomycin as initial therapy unclear; effective as step down



## Question #8

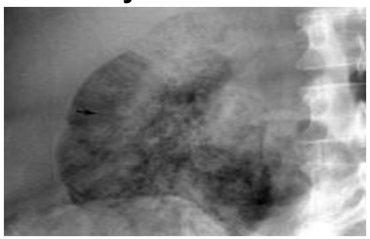
- 68-year-old diabetic man with CHF, vascular disease, BPH presented with 2 days of vomiting, abdominal pain, and confusion.
- Vital signs: T 99.9 BP 47/39, HR 110, RR 22
- Physical exam: patient was obtunded but appeared to have tenderness in the epigastric area
- Labs: WBC 23.7 (94% segs), platelets 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

## Question #8

**What would you order next?**

A. Abdominal ultrasound
B. Abdominal CT
C. Nasogastric tube
D. Stool for *C. diff* testing

**X-Ray of Abdomen**



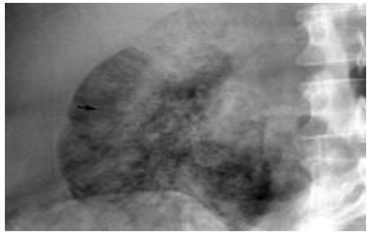

©2026 Infectious Disease Board Review, LLC

## Question #8

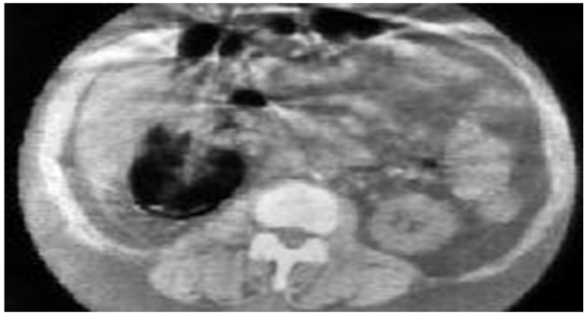
**What would you order next?**

A. Abdominal ultrasound
**B. Abdominal CT***
C. Nasogastric tube
D. Stool for *C. diff* testing

**X-Ray of Abdomen**



## Abdominal CT with Emphysematous Pyelonephritis



CT showing gas within the renal parenchyma

## Clinical Course of Question #8 Case

- 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

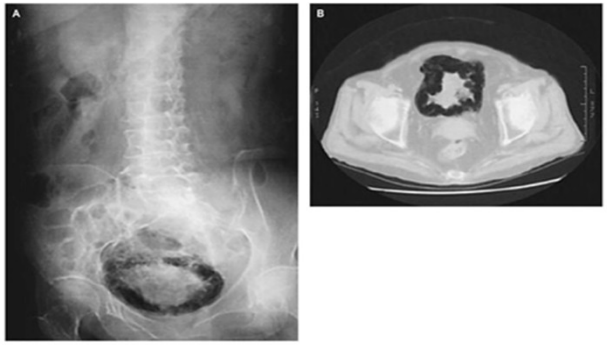
## Diagnosis and Management of Emphysematous Pyelonephritis

- 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


©2026 Infectious Disease Board Review, LLC

## Emphysematous Cystitis



Asada, NEJM 2003;349: 258

## Emphysematous Cystitis



Tzou, NEJM 2016: 375; 18

## Diagnosis and Management of Emphysematous Cystitis

- Female predilection
- Most cases in diabetics
- Commonly caused by *E. coli, Klebsiella (Candida* reported)
- Organisms produce gas in the bladder wall and lumen
- Can present with lower abdominal pain
- Diagnosed radiologically
- Relieve bladder obstruction if present
- Typically responds well to **medical management**

## Question #9

- 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


©2026 Infectious Disease Board Review, LLC

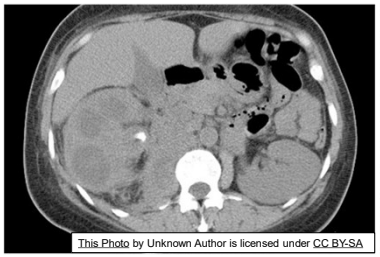
## Question #9

- 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

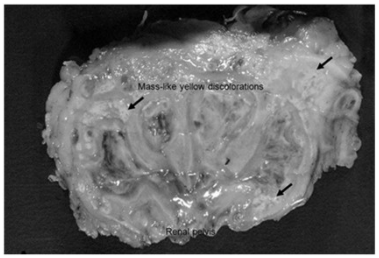
**In addition to CT scan, what will be the definitive therapy?**

A. Renal biopsy
B. 3-6 months of antibiotics based on current urine culture
C. Percutaneous drainage
**D. Nephrectomy* - can you name the diagnosis?**

## Xanthogranulomatous Pyelonephritis

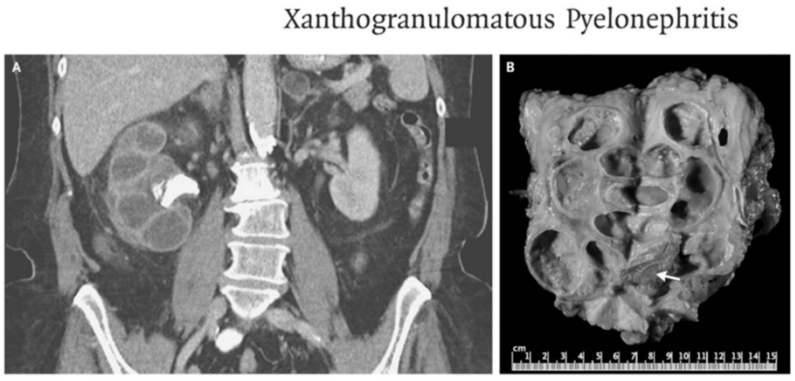


This Photo by Unknown Author is licensed under CC BY-SA




https://www.auanet.org/education/auauniversity/education-products-and-resources/pathology-for-urologists/kidney/inflammatory/necrotic-renal-lesions/xanthogranulomatous-pyelonephritis

## Bear Paw Sign




Marinacci, New England Journal of Medicine 2018; 378:10

## Xanthogranulomatous Pyelonephritis

- Chronic polymicrobial infection of renal parenchyma
- Often starts with stone/obstruction
- Frequently insidious and mistaken for tumor
- Renal tissue is destroyed and replaced by granulomatous tissue
- Yellow from the foam cells (macrophages) full of lipids
- **Requires nephrectomy** plus antibiotics
- Our patient underwent right nephrectomy, with finding of a variegated tan-white mass, large amount of inflammatory reaction, purulence in right renal fossa



©2026 Infectious Disease Board Review, LLC



## To Re-Cap

- Acute and recurrent cystitis in women-nitrofurantoin
- Asymptomatic bacteriuria
  - Pregnancy and urologic surgery: screen and treat
  - Everyone else—don't test the urine
- Catheter-associated UTI—ensure drainage
- Complicated UTI—apply the 4 steps
- Pyelonephritis—treat with tissue-active agent
- Urosepsis and worse
  - Emphysematous pyelonephritis-drainage
  - Emphysematous cystitis-medical management
  - Xanthogranulomatous pyelonephritis-removal

## Is Everything Clear Now?


- trautner@wustl.edu
- @bwtrautner






©2026 Infectious Disease Board Review, LLC

# New classifications of uUTI and cUTI

## Old Classifications

**Uncomplicated UTI:** Acute cystitis in afebrile nonpregnant premenopausal women with no diabetes and no urologic abnormalities



**Acute Pyelonephritis:** Acute kidney infection in women otherwise meeting the definition of uncomplicated UTI above



**Complicated UTI:** All other UTIs

## New Classifications

**Uncomplicated UTI: Infection confined to the bladder** in afebrile women or men

**Complicated UTI: infection beyond the bladder** in women or men

- Pyelonephritis
- Febrile or bacteremic UTI
- Catheter-associated (CAUTI)
- Prostatitis* (*not covered by these guidelines)



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# IDSA Cystitis Guidelines (2010)

## First-line Agents

- Nitrofurantoin
- Trimethoprim-sulfamethoxazole
- Fosfomycin
- Pivmecillinam

## 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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

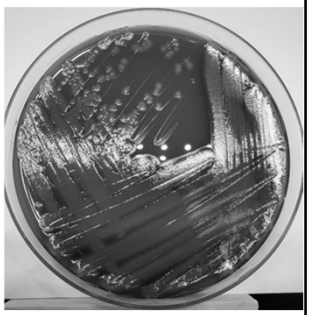
BID: twice daily; DS: double strength



©2026 Infectious Disease Board Review, LLC

# New Oral Drugs for Cystitis: FDA Approved for Uncomplicated UTI

- Pivmecillinam (Pivya)
  - Pro-drug of mecillinam
  - Binds to PBP-2 in Gram-negative cell wall
  - Effective against ESBL+ Enterobacterales, Staph saprophyticus
- Gepotidacin (Blujepa)
  - Blocks DNA topoisomerase
  - Effective against ESBL+ Enterobacterales, S. saprophyticus, and E. faecalis
  - Does not get into the prostate or kidneys
  - Also approved for gonorrhea
- Sulopenem etzadroxil/probenecid (Orlynvah)
  - Thiopenem—new beta-lactam class
  - Effective against ESBL+ Enterobacterales, S. saprophyticus
  - Did not get approval for complicated UTI



Not for *Pseudomonas* or VRE

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# 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 |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Mo: month; y: year

Nicolle et al, IDSA Guidelines for Asymptomatic Bacteriuria, Clin Inf Dis 2019


©2026 Infectious Disease Board Review, LLC

# 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<br>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 |

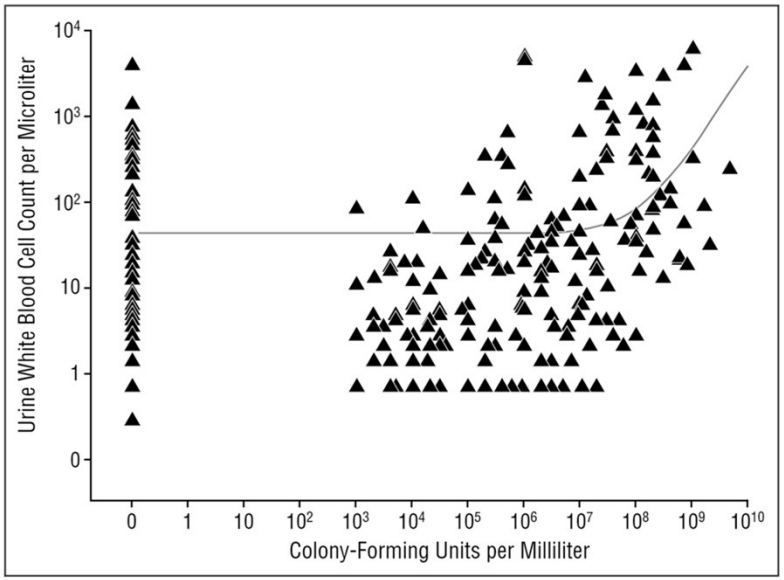
CTFPHC, Canadian Task Force on Preventive Health Care; USPSTF, United States Preventive Services Task Force

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Relationship Between Pyuria and Bacteriuria/Candiduria in Catheterized Patients




CFU: colony-forming unit

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 $10^8$

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Tambyah and Maki, Arch Intern Med. 2000 Mar 13;160(5):678-82 and 673-7



©2026 Infectious Disease Board Review, LLC

# Choice of Empiric Agent for cUTI

IDSA

| Condition of the Patient | Preferred | Alternative |
|---|---|---|
| **Sepsis** with or without shock | Third or fourth generation cephalosporins, carbapenems, piperacillin-tazobactam, fluoroquinolones | Novel beta lactam-beta lactamase inhibitors, cefiderocol, plazomicin, or older aminoglycosides |
| **Without sepsis, IV** route of therapy | Third or fourth generation cephalosporins, piperacillin-tazobactam, or fluoroquinolones | Carbapenems, newer agents (novel beta lactams-beta lactamase inhibitors, cefiderocol, plazomicin), or older aminoglycosides |
| **Without sepsis, oral** route of therapy | Fluoroquinolones or trimethoprim-sulfamethoxazole | Amoxicillin-clavulanate or oral cephalosporins |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# IDSA treatment approach

IDSA

**Step 1**

- **Consider severity of illness:**
  - Sepsis with shock, sepsis without shock, no sepsis

**Step 2**

- **Evaluate patient-specific risk factors for resistant organisms:**
  - Avoid antibiotics to which patient has had resistant pathogen previously isolated
  - Avoid fluoroquinolones (FQ) if patient exposed to FQ in past 12 months

**Step 3**

- **Assess other patient-specific factors:**
  - Risk of allergic reaction, contraindications, drug–drug interactions

**Step 4**

- **If septic use antibiogram to tailor empiric therapy:**
  - Consider at least 90% susceptibility threshold for sepsis with shock
  - Consider at least 80% susceptibility threshold for sepsis without shock
  - Patients not septic have lower (<5%) risk of mortality and initial inappropriate empiric choice has little impact on mortality

IDWeek

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

**Wednesday, August 26, 2026**

---

**52**

# Kitchen Sink: Syndromes Not Covered Elsewhere

**Stacey Rose, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Kitchen Sink: Syndromes Not Covered Elsewhere

**Stacey R. Rose, MD, FACP, FIDSA**
**Baylor College of Medicine**

9/7/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Session Plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)




## 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

4



©2026 Infectious Disease Board Review, LLC

## 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

## Question #1

**Which of the following tests will most likely yield the diagnosis?**

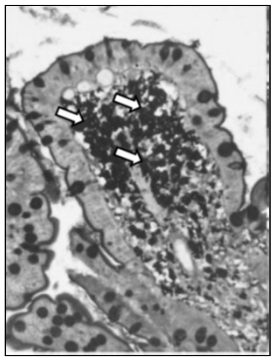
A. Anti-streptolysin O Antibody
B. Anti-nuclear Antibody
C. Stool ova and parasite
**D. Duodenal biopsy***



**Diagnosis: Whipple's disease**

## Whipple's Disease

- Caused by *Tropheryma whipplei* (gram variable bacterium, difficult to cultivate)
- More common in middle-aged white males
- 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.

## Whipple's: Clinical Presentations

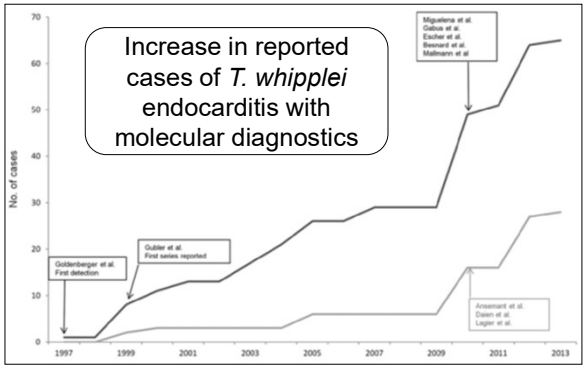
**TABLE 1** Clinical manifestations of *Tropheryma whipplei* infection[a]

| 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.


©2026 Infectious Disease Board Review, LLC

## Whipple's Endocarditis - Increasingly Recognized




- 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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Whipple's: Treatment

### No Gold Standard



*Symptoms improve, but relapse is common without prolonged treatment / suppression*

***Options:***

- Ceftriaxone or meropenem plus prolonged trimethoprim-sulfamethoxazole (~1 year)

OR

- Doxycycline plus hydroxychloroquine (12-18 mos)

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*

## Whipple's Disease
### Take Home Points



- Cause: *Tropheryma Whipplei*
- Epidemiology: middle-aged, white 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

## 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.


©2026 Infectious Disease Board Review, LLC

## Question #2

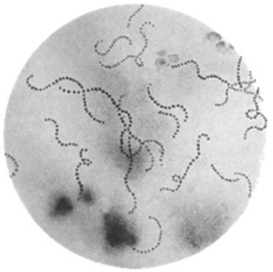
### Which of the following is the best explanation for her symptoms?

A. Acute HIV infection
B. Mononucleosis due to Epstein Barr Virus
C. Acute rheumatic fever
D. Lemierre's syndrome

## 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



*Streptococcus pyogenes* (group A *Streptococcus*) on Gram stain. Source: Public Health Image Library, CDC

## Explanation

✗ **Acute HIV** – joint symptoms not characteristic; HIV 4th gen testing should detect early infection

✗ **Mononucleosis due to EBV** – joint pains not characteristic; no mention of lymphadenopathy

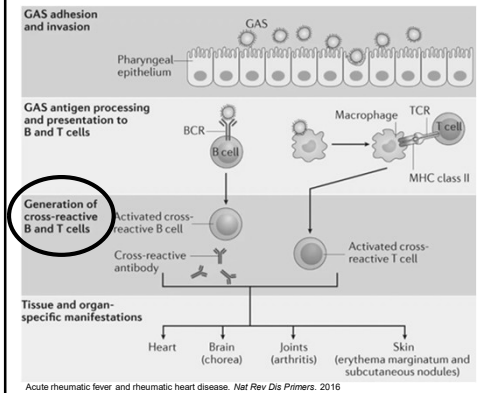
✓ **Acute Rheumatic fever** – multisystem disease following group A strep; meets Jones criteria

✗ **Lemierre's** – septic thrombophlebitis of internal jugular vein following pharyngitis, typically caused by *Fusobacterium necrophorum*; joint pains not characteristic, no neck swelling

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

15

## Acute Rheumatic Fever




Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers*. 2016

- 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* pharyngitis
- Leads to systemic manifestations (**arthritis**, **carditis**, **chorea**, **skin**)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

16



©2026 Infectious Disease Board Review, LLC

## 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

## 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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015

## Recognizing Acute Rheumatic Fever

- **Timing**: ~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.*

## Treatment and Prophylaxis of Acute Rheumatic Fever

| Primary Episode | Secondary Prophylaxis |
|---|---|
| IM benzathine penicillin x 1<br>OR<br>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.*

**52 Kitchen Sink: Syndromes Not Covered Elsewhere**
*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

## Duration of Secondary Prophylaxis Following Acute Rheumatic Fever:
## *Longest if Carditis and Residual Valvular Disease*

| 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 |

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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Acute Rheumatic Fever
## Take Home Points



- 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)

## 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.

## Question #3

**Which of the following treatments are recommended?**

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
D. Botulinum antitoxin


©2026 Infectious Disease Board Review, LLC

## Question #3

**Which of the following treatments are recommended?**

A. Plasmapheresis
B. Naloxone
C. Tetanus antitoxin
**D. Botulinum antitoxin***

## Explanation



Tetanus: sardonic smile



Botulism: ptosis

✗ Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)

✗ Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)

✗ Tetanus antitoxin – for tetanus (rigid paralysis)

✓ Botulinum antitoxin – for botulism (flaccid paralysis)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltex
https://www.nejm.org/doi/pdf/10.1056%2FNEJMicm1003352

## Botulism



https://phil.cdc.gov/details.aspx?pid=2107

- Caused by **Clostridium botulinum* (gram positive, strict anaerobe with subterminal spore; found in soil)
- Toxin prevents 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*

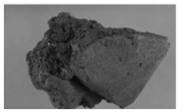
## Botulism



**Foodborne**

**Infant**





**Wound (black-tar heroin)**

**Iatrogenic**



Peak CM, Rosen H, Kamali A, et al. Wound Botulism Outbreak Among Persons Who Use Black Tar Heroin — San Diego County, California, 2017–2018. MMWR 2019.
https://www.cdc.gov/botulism/hcp/clinical-overview/index.html; *Principles and Practice of Infectious Diseases, 9th ed.*



©2026 Infectious Disease Board Review, LLC

***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

# Botulism Treatment

| Supportive Care | Antitoxin |
|---|---|
| • Ventilatory support for respiratory compromise<br>• Wound debridement | • Administer Botulinum anti-toxin (BAT) asap to prevent progression<br>• 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*

# Botulism
## Take Home Points



- **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

# Question #4



- A 34-year-old motorcyclist is involved in a severe motor vehicle accident, resulting in laceration of the spleen and requiring splenectomy


©2026 Infectious Disease Board Review, LLC

## Question #4

**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*

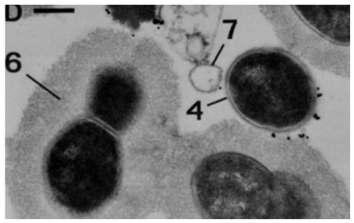
## Question #4

**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*

## Splenectomy and Infection Risk

- **Why:** reduced clearance of encapsulated organisms; impaired humoral immunity



Skov Sørensen et al. (1988) Infect Immun 56: 1890-1896

**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

## Strategies to Reduce Infection Risk in Asplenia




**Vaccination for Encapsulated Organisms**
- Pneumococcus
- Meningococcus
- Hemophilus influenza Type B (HiB)

**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


©2026 Infectious Disease Board Review, LLC

## Infection in Asplenia
### Take Home Points



- 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

## Question #5



At Clinical Presentation



1 Week After Discharge

- A 19-year-old male presents with **fever**, **tachycardia**, and **hypotension**. On examination, he is found to have two **skin abscesses** in the pubic region, as well diffuse **erythroderma** most notable on the palms.
- Laboratory analyses show **leukocytosis**, **anemia**, **transaminitis**, and **acute kidney injury**. Chest X-ray shows small bilateral **pleural effusions**.
- He is treated with intravenous fluids, inotropic support and empiric broad-spectrum antibiotics. Incision and drainage of the skin abscesses is performed; cultures grow **Methicillin Sensitive Staphylococcus Aureus (MSSA).**
- 1 week after discharge, he develops **skin peeling** on his palms (see images).

J Family Med Prim Care 2022;11:4837-40.

## Question #5



At Clinical Presentation



1 Week After Discharge

**The patient's clinical syndrome was most likely caused by which of the following?**

A. Pyrogenic toxin superantigen
B. Bacterial endotoxin
C. Cereulide toxin
D. Aflatoxin

J Family Med Prim Care 2022;11:4837-40.

## Question #5



At Clinical Presentation



1 Week After Discharge

**The patient's clinical syndrome was most likely caused by which of the following?**

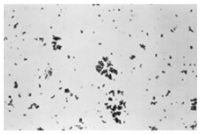
**A. Pyrogenic toxin superantigen***
B. Bacterial endotoxin
C. Cereulide toxin
D. Aflatoxin

J Family Med Prim Care 2022;11:4837-40.


©2026 Infectious Disease Board Review, LLC

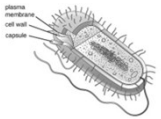
## Explanation

Pyrogenic toxin superantigen - cause of toxic shock syndrome (see next slide)

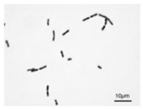


wwwn.cdc.gov/phil/Details.aspx?pid=5147

Bacterial endotoxin e.g., lipopolysaccharide (LPS) - gram negative cell wall component that can trigger systemic inflammation



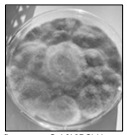

commons.wikimedia.org/wiki/File:OSC_Microbio_03_03_Capsules.jpg



commons.wikimedia.org/wiki/File:Bacillus_cereus_Gram.jpg

Cereulide toxin - produced by *Bacillus cereus*, cause of food poisoning / emesis

Aflatoxin - produced by toxigenic molds e.g., *Aspergillus flavus*, exposure to large quantity can lead to liver injury



commons.wikimedia.org/wiki/File:Aspergillus_flavus_sur_Sab%2BChl.jpg

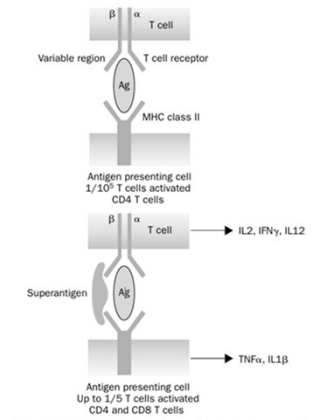



*Figure 1. Contrasting mechanisms of conventional antigen (upper panel) and superantigen presentation (lower panel).*

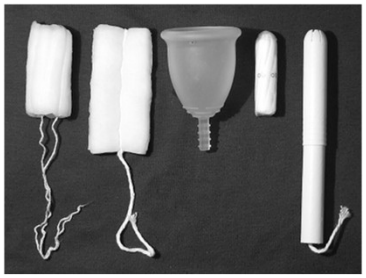
## Staphylococcal Toxic Shock Syndrome (TSS)

- Bacteria produces **pyrogenic toxin superantigen** (e.g., TSST-1, Staphylococcal Enterotoxin B)
- Superantigen stimulates MHC class II and T cell receptor on antigen presenting cells in a way that bypasses traditional mechanism of activation
- **Activates a large number of T cells at the same time → cytokine "storm"**

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Superantigens: microbial agents that corrupt immunity. Lancet Infect Dis. 2002

## Risk Factors for Staphylococcal TSS



https://commons.wikimedia.org/wiki/File:Fleurcup_and_tampons.jpg

- Colonization or infection with **toxin-producing strains** (MSSA > MRSA)
- **Menstrual**: use of tampons; also associated with menstrual cups
- **Non-menstrual**: skin infection, burns, surgery

## Clinical Features

## 4 Criteria - *Probable*

## 5 Criteria - *Confirmed*

***Panel 1*: Staphylococcal toxic shock syndrome clinical case definition**

1 Fever ≥38·9°C
2 Rash—diffuse macular erythroderma
3 Desquamation—1–2 weeks after onset of illness, especially of palms and soles
4 Hypotension—systolic blood pressure ≤90 mm Hg for adults
5 Multi-system involvement—3 or more of the following:
  a Gastrointestinal—vomiting or diarrhoea at the onset of illness
  b Muscular—severe myalgia or elevated creatine phosphokinase
  c Mucous membranes—vaginal, oropharyngeal, conjunctival hyperaemia
  d Renal—blood urea nitrogen or creatinine twice-upper limit of normal
  e Hepatic—total bilirubin twice-upper limit of normal
  f Haematological—platelets ≤$100\times10^9$/L
  g CNS—disorientation or alterations in consciousness without focal neurological signs
6 Negative results on the following tests:
  a Blood, throat, or cerebrospinal fluid culture (blood culture may be positive for *S aureus*)
  b Rise in titre to Rocky Mountain spotted fever, leptospirosis, or measles

**Case classification**
Probable: case with five of the six clinical findings described
Confirmed: case with all six of the clinical findings described

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Gram-positive toxic shock syndromes. Lancet Infect Dis. 2009



©2026 Infectious Disease Board Review, LLC

## Treatment


https://en.wikipedia.org/wiki/Clindamycin

**<u>Anti-staphylococcal Antibiotic</u>:**

- No risk factor for MRSA: **oxacillin** or **nafcillin** or **cefazolin**
- MRSA risk factor: **vancomycin** or **daptomycin**

PLUS

**<u>Anti-toxin Agent</u>**: **clindamycin** or **linezolid**

PLUS

**<u>Source Control</u>**

Toxic Shock Syndrome: A Literature Review. Antibiotics (Basel). 2024

## Staphylococcal TSS
### Take Home Points



- **Epidemiology**: *menstrual* – tampon or menstrual cup use; *non-menstrual* – colonization or infection with toxin-producing strain, burns, surgery
- **Clinical presentation**: fever, rash (erythroderma), desquamation after 1-2 weeks; hypotension; multi-system involvement (suspect in sepsis-like picture)
- **Diagnosis:** clinical; can confirm with isolation of toxin
- **Treatment**: anti-staphylococcal antibiotic plus anti-toxin antibiotic (clindamycin or linezolid) plus source control

## Question #6

- WBC 11 x $10^9$ / L (high) with 85% neutrophils
- Hgb 13.6 g/dL (normal)
- Platelets 460,000 / mcL (high)
- Cr 1.3 mg/dL (high)
- Na 136 meq/L, K 4.0 meq/L (normal)
- ALT 30, AST 33 U/L (normal)
- Total bilirubin 2.0 mg/dL (high)
- Alkaline phosphatase 190 U/L (high)

- A 65-year-old male undergoes partial colectomy for colon cancer.
- His convalescence is complicated, requiring ICU stay and total parenteral nutrition.
- On hospital day #11, he develops acute onset of fever and hypotension without localizing symptoms. The surgical site is benign-appearing.
- Notable labs are as shown. Blood and urine cultures and drawn, and the patient is started on empiric broad spectrum antibiotics.
- Bedside right upper quadrant ultrasound is performed and shows gall bladder wall thickening without dilation of the common bile duct, and Murphy's sign is negative.

## Question #6

**Which of the following describes the best next step in management?**

A. Computed tomography (CT) abdomen / pelvis
B. CT with PE protocol
C. Hepatic iminodiacetic acid scan (HIDA)
D. Diagnostic laparoscopy

Indian J Dermatol. 2010;55(1):79-85.

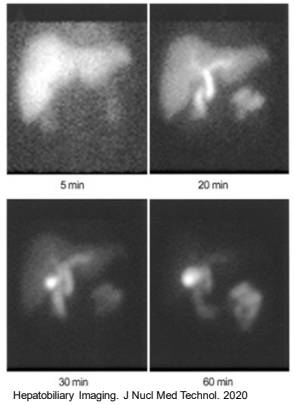

©2026 Infectious Disease Board Review, LLC

## Question #6

**Which of the following describes the best next step in management?**

A. Computed tomography (CT) abdomen / pelvis
B. CT with PE protocol
**C. Hepatic iminodiacetic acid scan (HIDA)***
D. Diagnostic laparoscopy

Indian J Dermatol. 2010;55(1):79-85.



Hepatobiliary Imaging. J Nucl Med Technol. 2020

Normal HIDA Scan Showing Radiotracer In Gall Bladder

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

- ✓ **HIDA scan: most sensitive and specific**, non-invasive, safe in renal dysfunction, advised if ultrasound is non-diagnostic
- ✗ CT scan: high sensitivity and can rule out other abdominal pathology, but contrast not advised in renal dysfunction
- ✗ MRI: most useful if suspect choledocholithiasis but not ideal in renal dysfunction
- ✗ Exploratory laparotomy: too invasive

## Acute Acalculous Cholecystitis: Epidemiology

- **Pathophysiology**:
  - Fasting → **inhibited emptying of gallbladder** → bile stasis / toxicity
  - Ischemic injury due to vascular constriction or obstruction
- **Risk Factors**:
  - Surgery
  - Trauma
  - Total parenteral nutrition
  - Burn injury
  - Ischemic heart disease
  - Infections

**Bacterial:** *Brucella, Coxiella, Leptospira, Orientia tsutsugamushi, M. Tuberculosis, Salmonella, Vibrio cholerae*

**Fungal:** Candida spp

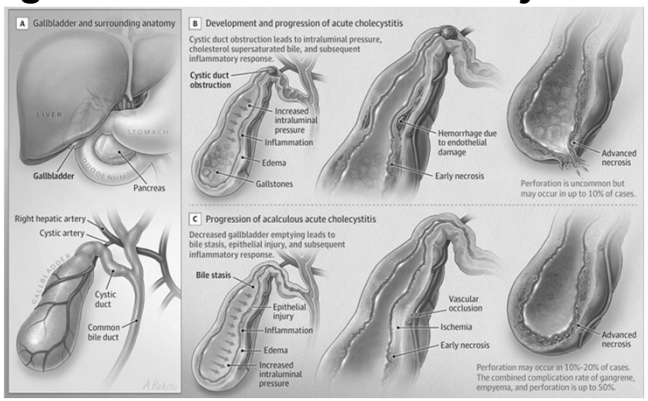
**Parasitic:** Cyclospora, Microsporidia, Malaria, Schistosomiasis, Echinococcus (obstruction)

**Viral**: CMV, Dengue

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Acute Acalculous Cholecystitis. Curr Treat Options Gastroenterol. 2005

## Diagnosis: *Acalculous cholecystitis*




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Acute Cholecystitis: A Review. JAMA. 2022


©2026 Infectious Disease Board Review, LLC

## Clinical Presentation and Treatment

Presentation more **subtle** than for calculous cholecystitis;
**RUQ pain** only present in ~25%

Consider diagnosis in critically ill patient with unexplained **fever**, **leukocytosis**, **elevated liver function tests**

**Treat with perioperative antibiotics:** ampicillin / sulbactam or piperacillin / tazobactam

**PLUS** laparoscopic **cholecystectomy** or percutaneous **cholecystostomy** (if not surgical candidate)

Acute Acalculous Cholecystitis. Curr Treat Options Gastroenterol. 2005; Acute Cholecystitis: A Review. JAMA. 2022;Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018l Surgical Infection Society Guidelines for Antibiotic Use in Patients Undergoing Cholecystectomy for Gallbladder Disease. Surg Infect (Larchmt). 2022

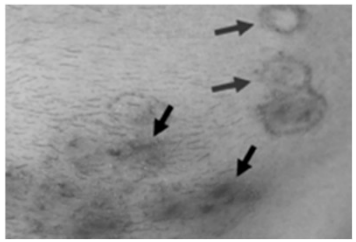
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Acalculous Cholecystitis
### Take Home Points



- **Risk factors**: surgery, trauma, TPN, burns, ischemia, infections
- **Diagnosis**: subtle presentation; consider if unexplained fever / leukocytosis / elevated LFT's in critically ill patient.
  - Confirm with ultrasound → HIDA scan
- **Treatment**: broad-spectrum antibiotics (ampicillin / sulbactam or piperacillin / tazobactam), then laparoscopic cholecystectomy or percutaneous cholecystostomy (if not surgical candidate)

## Question #7



- A 35-year-old male businessman presents with new skin lesions on the trunk, buttocks and extremities. The lesions are pruritic and he is concerned they are spreading.
- He is otherwise healthy. He does not smoke, drinks socially and engages in sexual contact with men; he takes pre-exposure prophylaxis for HIV and uses doxycycline for post-exposure prophylaxis if / when he engages in unprotected intercourse.
- He recently traveled to Paris, France for a work conference.
- Skin lesions are as pictured. Exam is also notable for inguinal lymphadenopathy.

Indian J Dermatol. 2010;55(1):79-85.

## Question #7

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

A. Condyloma lata (syphilis)
B. Bacterial folliculitis
C. Trichophyton rubrum
D. Trichophyton mentagrophytes genotype VII

Indian J Dermatol. 2010;55(1):79-85.



©2026 Infectious Disease Board Review, LLC

## Question #7

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

A. Condyloma lata (syphilis)
B. Bacterial folliculitis
C. Trichophyton rubrum
**D. Trichophyton mentagrophytes genotype VII***

Indian J Dermatol. 2010;55(1):79-85.

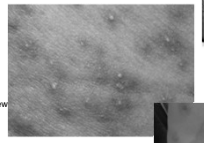
## Explanation



Extensive Condyloma Lata Lesions in Unusual Sites: An Atypical Manifestation of Secondary Syphilis. Case Rep Med. 2025

Condyloma lata (syphilis)

Bacterial folliculitis



https://www.pcds.org.uk/clinical-guidance/folliculitis-an-overview

Trichophyton rubrum: most common cause of tinea corporis



https://commons.wikimedia.org/wiki/File:Tinea_corporis.jpg

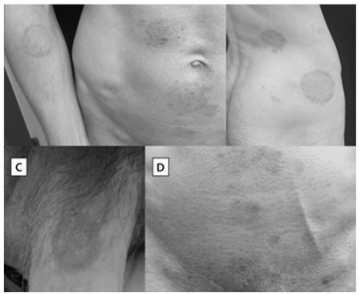
Trichophyton mentagrophytes genotype VII: Sexual transmission, MSM



https://www.cdc.gov/mmwr/volumes/73/wr/mm7343a5.htm

## Trichophyton Mentagrophytes Genotype VII (TMVII)

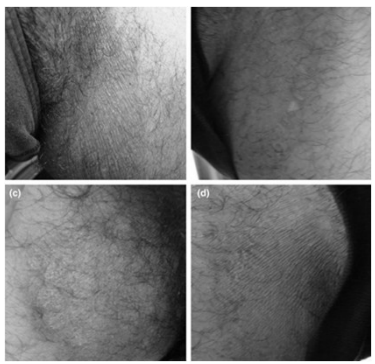
- First described in travelers returning from Southeast Asia; now in Europe, US
- Mostly in men who have sex with men **(MSM) / sexual transmission**
- **Clinical Features**:
  - Lesions located on genital, perianal, perioral / facial, trunk / extremities
  - Superficial or subcutaneous / purulent
  - 1/3 with lymphadenopathy
  - **Pain and itching** common (>75%)
- **Treatment**: oral **terbinafine** until symptoms resolve (up to 3 months); counsel re: transmission risk




Trichophyton mentagrophytes type VII: cohort study on patient characteristics, clinical features, disease course, and treatment. J Dtsch Dermatol Ges. 2025; *Notes from the Field: Trichophyton mentagrophytes* Genotype VII — New York City, April–July 2024. MMWR Morb Mortal Wkly Rep 2024;73:985–988.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Another Emerging Infection with Reported Sexual Transmission: *Trichophyton indotineae*




- First identified in India, now reported in > 40 countries
- Equally affects men and women
- Person to person contact; sexual transmitted reported (rare)
- Antifungal resistance common; optimal treatment not defined

Trichophyton indotineae: Epidemiology, antifungal resistance and antifungal stewardship strategies. J Eur Acad Dermatol Venereol. 2026



©2026 Infectious Disease Board Review, LLC

## Trichophyton Mentagrophytes Genotype VII (TMVII)
### Take Home Points



- **Risk factors**: MSM
- **Diagnosis**: clinical; typically superficial, ringworm-like lesions on **genital** / **perianal** / **perioral** areas but can be subcutaneous / pustular with lymphadenopathy. **Pain**, **itching** common.
- **Treatment**: oral **terbinafine** for ~3 months



## Kitchen Sink Summary

## Kitchen Sink Summary - 1

**Whipple's**:
- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- Or PCR of tissue (heart valve for endocarditis)



**Acute Rheumatic Fever**:
- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html

## Kitchen Sink Summary - 2

**Botulism**:
- Due to C. botulinum toxin
- Food; infant; wound (black-tar heroin); iatrogenic
- Descending flaccid paralysis (starts with cranial nerves)
- Antitoxin / supportive care



**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 vaccines and PCN prophylaxis (< 5 yrs old; recent splenectomy; prior episodes of sepsis)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

**52 Kitchen Sink: Syndromes Not Covered Elsewhere**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

## Kitchen Sink Summary - 3

**Staphylococcal toxic shock syndrome**

- Menstrual and non-menstrual risk factors
- **Clinical criteria**: fever, rash (erythroderma), desquamation after 1-2 weeks; hypotension; multi-system involvement
- **Treatment**: anti-staphylococcal antibiotic plus anti-toxin antibiotic (clindamycin or linezolid) plus source control

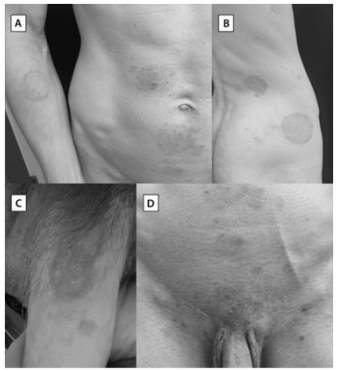


**Acalculous cholecystitis**

- **Risk factors**: surgery, trauma, TPN, burns, ischemia, infections
- Suspect in critically ill patient with unexplained fever / leukocytosis / elevated LFT's; confirm with ultrasound or HIDA
- **Treatment**: antibiotics + laparoscopic cholecystectomy or percutaneous cholecystostomy (if poor surgical candidate)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Kitchen Sink Summary - 4




**Trichophyton mentagrophytes genotype VII (TMVII):**

- Emerging sexually transmitted fungal infection
- Suspect in MSM with painful, itchy "ringworm" lesions in genital / perianal / perioral areas (though can be subcutaneous / pustular with lymphadenopathy)
- Treat with oral terbinafine for ~3 months

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



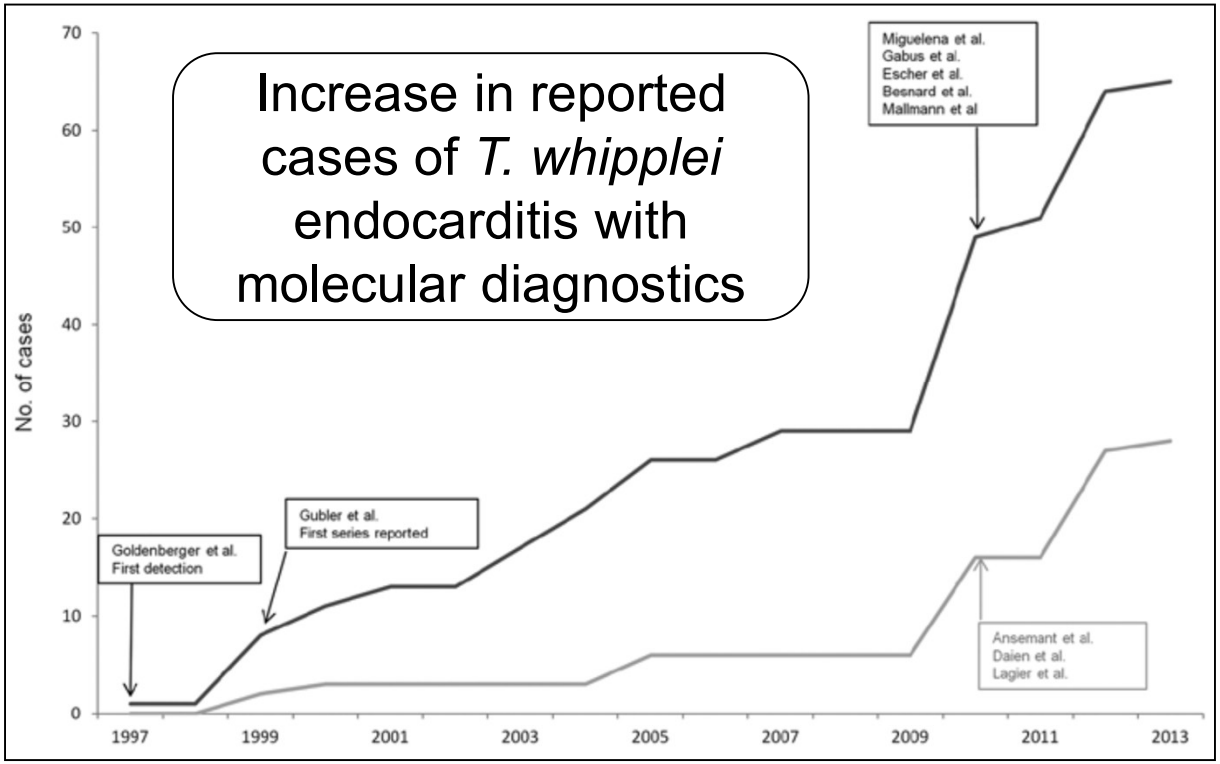
## Questions?

**Stacey Rose, MD, FACP, FIDSA**
**srrose@bcm.edu**



©2026 Infectious Disease Board Review, LLC

# Whipple's Endocarditis - Increasingly Recognized




- 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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Explanation



**Acute HIV** – joint symptoms not characteristic; HIV 4th gen testing should detect early infection



**Mononucleosis due to EBV** – joint pains not characteristic; no mention of lymphadenopathy



**Acute Rheumatic fever** – multisystem disease following group A strep; meets Jones criteria



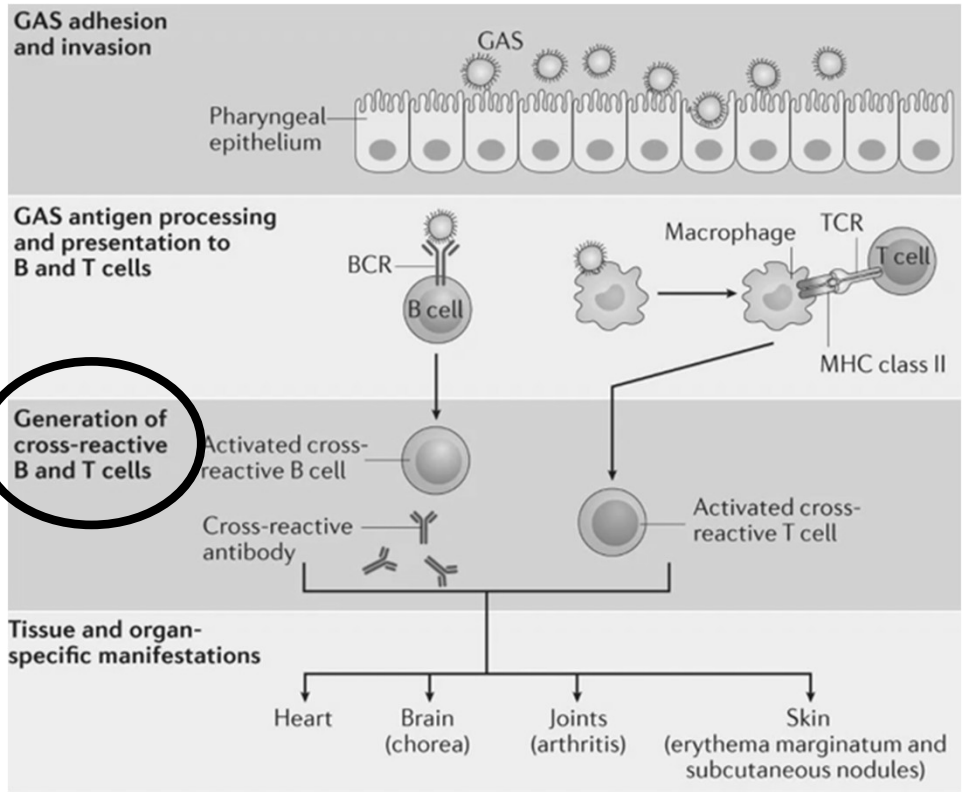
**Lemierre's** – septic thrombophlebitis of internal jugular vein following pharyngitis, typically caused by *Fusobacterium necrophorum*; joint pains not characteristic, no neck swelling

15

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Acute Rheumatic Fever




Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers*. 2016

- 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* pharyngitis
- Leads to systemic manifestations (**arthritis**, **carditis**, **chorea**, **skin**)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION





©2026 Infectious Disease Board Review, LLC

# 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)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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



©2026 Infectious Disease Board Review, LLC

# Duration of Secondary Prophylaxis Following Acute Rheumatic Fever:
## ***Longest if Carditis and Residual Valvular Disease***

| 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 |

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*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Explanation



Tetanus: sardonic smile



Botulism: ptosis

✗ Plasmapheresis – for Lambert-Eaton syndrome, immune attack of neuromuscular junction (chronic; associated with lung cancer)

✗ Naloxone – for opioid intoxication (respiratory suppression, *constricted* pupils)

✗ Tetanus antitoxin – for tetanus (rigid paralysis)

✓ Botulinum antitoxin – for botulism (flaccid paralysis)

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31137-7/fulltex
https://www.nejm.org/doi/pdf/10.1056%2FNEJMicm1003352

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

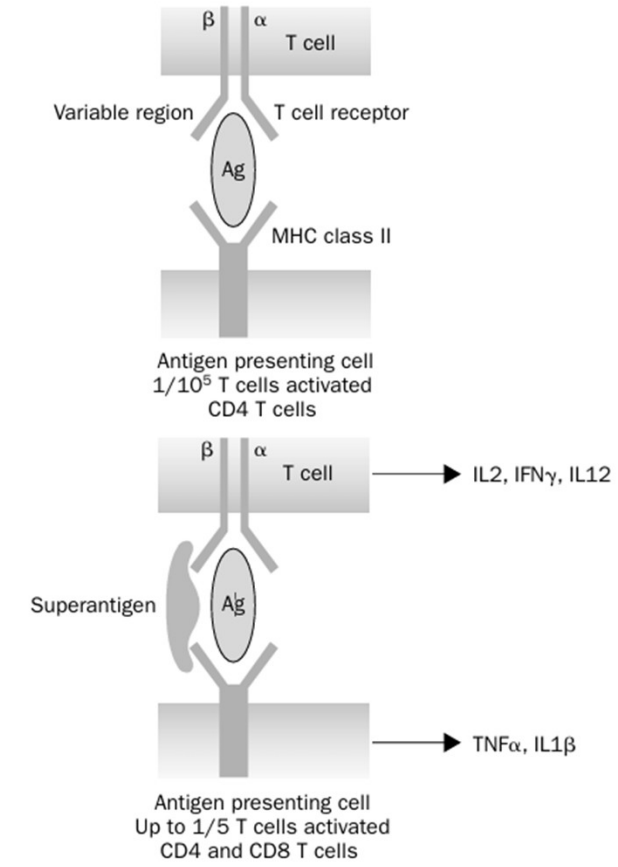



*Figure 1. Contrasting mechanisms of conventional antigen (upper panel) and superantigen presentation (lower panel).*

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# Staphylococcal Toxic Shock Syndrome (TSS)

- Bacteria produces **pyrogenic toxin superantigen** (e.g., TSST-1, Staphylococcal Enterotoxin B)
- Superantigen stimulates MHC class II and T cell receptor on antigen presenting cells in a way that bypasses traditional mechanism of activation
- **Activates a large number of T cells at the same time → cytokine "storm"**

Superantigens: microbial agents that corrupt immunity. Lancet Infect Dis. 2002


©2026 Infectious Disease Board Review, LLC

# Clinical Features

# 4 Criteria - *Probable*

# 5 Criteria - *Confirmed*

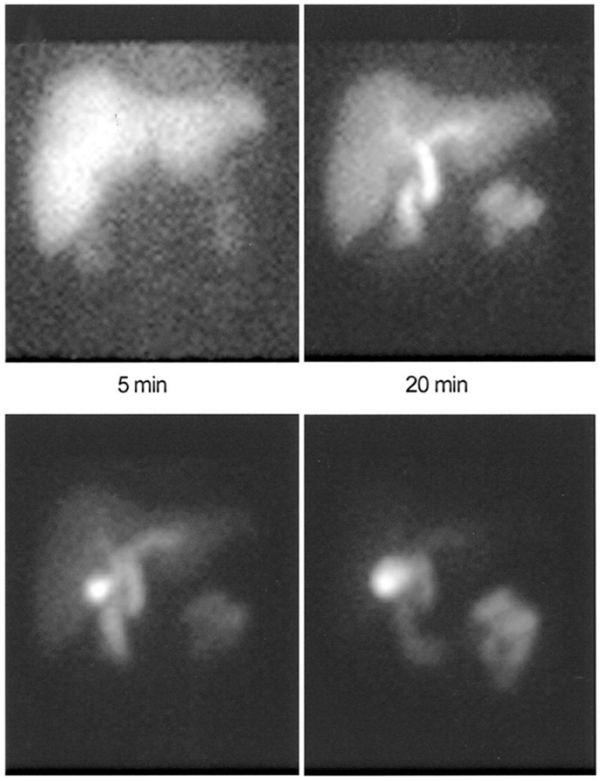
***Panel 1*: Staphylococcal toxic shock syndrome clinical case definition**

1 Fever ≥38·9°C
2 Rash—diffuse macular erythroderma
3 Desquamation—1–2 weeks after onset of illness, especially of palms and soles
4 Hypotension—systolic blood pressure ≤90 mm Hg for adults
5 Multi-system involvement—3 or more of the following:
  a Gastrointestinal—vomiting or diarrhoea at the onset of illness
  b Muscular—severe myalgia or elevated creatine phosphokinase
  c Mucous membranes—vaginal, oropharyngeal, conjunctival hyperaemia
  d Renal—blood urea nitrogen or creatinine twice-upper limit of normal
  e Hepatic—total bilirubin twice-upper limit of normal
  f Haematological—platelets ≤$100\times10^9$/L
  g CNS—disorientation or alterations in consciousness without focal neurological signs
6 Negative results on the following tests:
  a Blood, throat, or cerebrospinal fluid culture (blood culture may be positive for *S aureus*)
  b Rise in titre to Rocky Mountain spotted fever, leptospirosis, or measles

**Case classification**
Probable: case with five of the six clinical findings described
Confirmed: case with all six of the clinical findings described

SEE ENLARGED SLIDE FOLLOWING ENTIRE


©2026 Infectious Disease Board Review, LLC




Hepatobiliary Imaging. J Nucl Med Technol. 2020

Normal HIDA Scan Showing Radiotracer In Gall Bladder

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

- ✓ **HIDA scan: most sensitive and specific**, non-invasive, safe in renal dysfunction, advised if ultrasound is non-diagnostic
- ✗ CT scan: high sensitivity and can rule out other abdominal pathology, but contrast not advised in renal dysfunction
- ✗ MRI: most useful if suspect choledocholithiasis but not ideal in renal dysfunction
- ✗ Exploratory laparotomy: too invasive


©2026 Infectious Disease Board Review, LLC

# Acute Acalculous Cholecystitis: Epidemiology

- **Pathophysiology**:
  - Fasting → **inhibited emptying of gallbladder** → bile stasis / toxicity
  - Ischemic injury due to vascular constriction or obstruction
- **Risk Factors**:
  - Surgery
  - Trauma
  - Total parenteral nutrition
  - Burn injury
  - Ischemic heart disease
  - Infections

**Bacterial:** *Brucella, Coxiella, Leptospira, Orientia tsutsugamushi, M. Tuberculosis, Salmonella, Vibrio cholerae*

**Fungal:** Candida spp

**Parasitic:** Cyclospora, Microsporidia, Malaria, Schistosomiasis, Echinococcus (obstruction)

**Viral**: CMV, Dengue

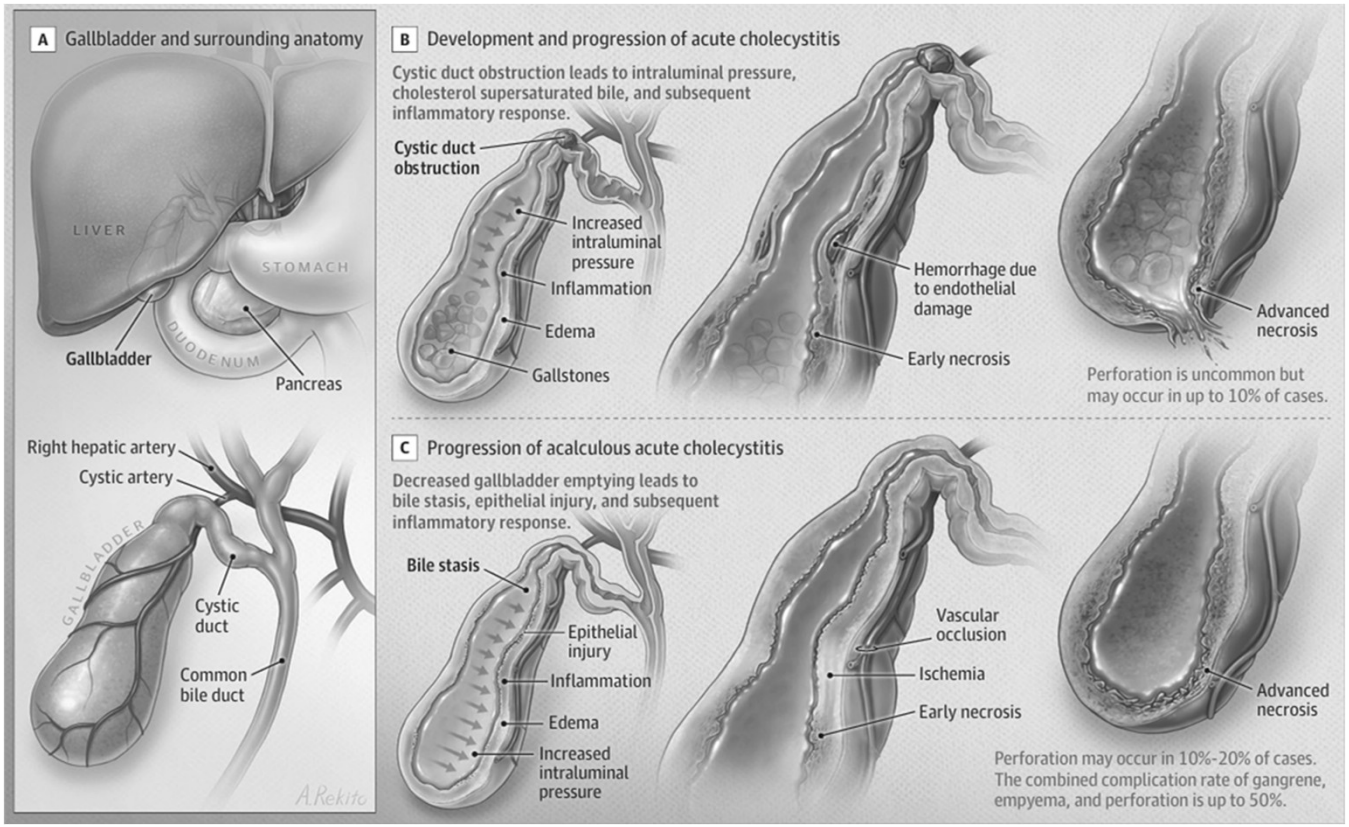
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Acute Acalculous Cholecystitis. Curr Treat Options Gastroenterol. 2005



©2026 Infectious Disease Board Review, LLC

# Diagnosis: *Acalculous cholecystitis*




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Acute Cholecystitis: A Review. JAMA. 2022



©2026 Infectious Disease Board Review, LLC

# Clinical Presentation and Treatment

Presentation more **subtle** than for calculous cholecystitis;
**RUQ pain** only present in ~25%

Consider diagnosis in critically ill patient with unexplained
**fever**, **leukocytosis**, **elevated liver function tests**

**Treat with perioperative antibiotics:** ampicillin /
sulbactam or piperacillin / tazobactam

**PLUS** laparoscopic **cholecystectomy** or percutaneous
**cholecystostomy** (if not surgical candidate)

Acute Acalculous Cholecystitis. Curr Treat Options Gastroenterol. 2005; Acute Cholecystitis: A Review. JAMA. 2022;Tokyo Guidelines 2018: antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2018l Surgical Infection Society Guidelines for Antibiotic Use in Patients Undergoing Cholecystectomy for Gallbladder Disease. Surg Infect (Larchmt). 2022

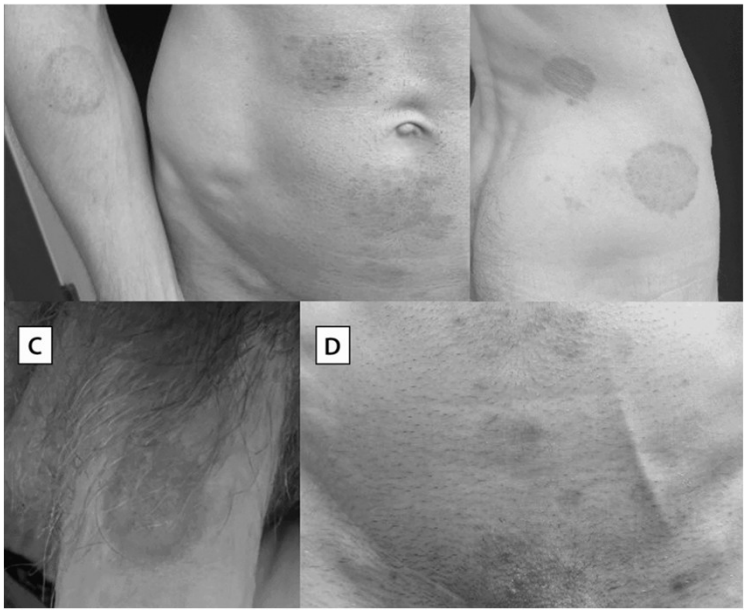
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION



©2026 Infectious Disease Board Review, LLC

# Trichophyton Mentagrophytes Genotype VII (TMVII)

- First described in travelers returning from Southeast Asia; now in Europe, US
- Mostly in men who have sex with men **(MSM) / sexual transmission**
- **Clinical Features**:
  - Lesions located on genital, perianal, perioral / facial, trunk / extremities
  - Superficial or subcutaneous / purulent
  - 1/3 with lymphadenopathy
  - **Pain and itching** common (>75%)
- **Treatment**: oral **terbinafine** until symptoms resolve (up to 3 months); counsel re: transmission risk




Trichophyton mentagrophytes type VII: cohort study on patient characteristics, clinical features, disease course, and treatment. J Dtsch Dermatol Ges. 2025; *Notes from the Field: Trichophyton mentagrophytes* Genotype VII — New York City, April–July 2024. MMWR Morb Mortal Wkly Rep 2024;73:985–988.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Kitchen Sink Summary - 1

**Whipple's**:

- Classic: arthralgia, diarrhea, weight loss
- Dx with duodenal bx (PAS+, foamy macrophages)
- Or PCR of tissue (heart valve for endocarditis)



**Acute Rheumatic Fever**:

- Kids / young adults with migratory polyarthritis, carditis, chorea, subcutaneous nodules, erythema marginatum following GAS pharyngitis
- Monthly IM penicillin prophylaxis for 10 years or to age 40 if carditis + residual valvular disease

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/groupastrep/diseases-public/rheumatic-fever.html



©2026 Infectious Disease Board Review, LLC

# 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



**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 vaccines and PCN prophylaxis (< 5 yrs old; recent splenectomy; prior episodes of sepsis)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Kitchen Sink Summary - 3

**Staphylococcal toxic shock syndrome**

- Menstrual and non-menstrual risk factors
- **Clinical criteria**: fever, rash (erythroderma), desquamation after 1-2 weeks; hypotension; multi-system involvement
- **Treatment**: anti-staphylococcal antibiotic plus anti-toxin antibiotic (clindamycin or linezolid) plus source control



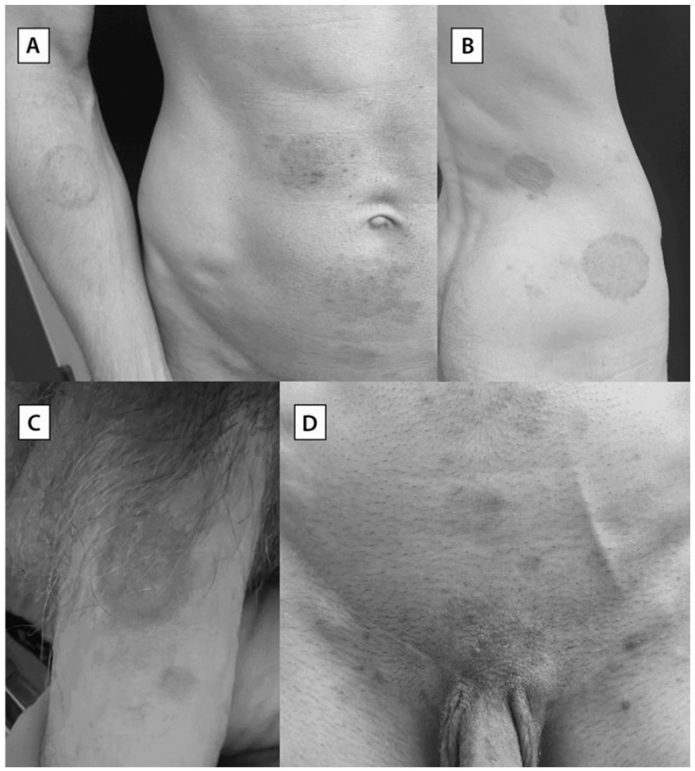
**Acalculous cholecystitis**

- **Risk factors**: surgery, trauma, TPN, burns, ischemia, infections
- Suspect in critically ill patient with unexplained fever / leukocytosis / elevated LFT's; confirm with ultrasound or HIDA
- **Treatment**: antibiotics + laparoscopic cholecystectomy or percutaneous cholecystostomy (if poor surgical candidate)

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

# Kitchen Sink Summary - 4




**<u>Trichophyton mentagrophytes genotype VII (TMVII)</u>:**

- Emerging sexually transmitted fungal infection
- Suspect in MSM with painful, itchy “ringworm” lesions in genital / perianal / perioral areas (though can be subcutaneous / pustular with lymphadenopathy)
- Treat with oral terbinafine for ~3 months

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION


©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL1

# How to Prepare for the Certification and Recertification, Including the LKA

**Helen Boucher, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

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

## Disclosures

- **Editor**
  - **ID Clinics of North America**
  - **Sanford Guide**

2

## 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

## Infectious Diseases Certification

- **Initial Certification Exam**
- **Maintenance of Certification – 2 Options:**
  - **Every 10 year MOC exam**
    - **Offered 1x/year – Oct 15, 2026, Oct 26, 2027**
  - **Longitudinal Knowledge Assessment (LKA)**
    - **Began 2023**

**https://www.abim.org/maintenance-of-certification/assessment-information/infectious-disease**

4

**OL1 How to Prepare for the Certification and Recertification, Including the LKA**
*Speaker: Helen Boucher, MD, FACP, FIDSA, (Hon) FRCPI*

©2026 Infectious Disease Board Review, LLC

## Certification Exams – Initial and MOC

- 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

5

## 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
- Five minutes to answer online
  - Open book
  - Correct answer and rationale provided
- Must answer 100 Q's per year (out of 120)
- CME: 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 2,486 ID physicians enrolled

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

6

## Longitudinal Knowledge Assessment (LKA)

- **Cost:** included in annual ABIM MOCA fee: $220 for ID only, $340 for two certificates, such as ID and Internal Medicine
- **Time Requirement:** an hour or more every three months to answer 30 questions per quarter. Up to 5 minutes per question + extra minutes from your "time bank", extra minutes allotted yearly. Must answer 100 of 120 questions per year. Opened but unanswered questions are scored as wrong
- **Resources:** can use anything but people, such as books, notes, or online resources including AI
- **Equipment:** good wireless connection, laptop or desktop display needed for questions with pictures
- **Feedback:** after each question is answered, the correct answer and rationale is shown. You cannot go back to answers later. Your score is provided quarterly after first year and compared to group. Pass/fail provided end of fifth year

7

## Longitudinal Knowledge Assessment (LKA®) Quarterly Question Schedule (with deadlines)

| QUARTER | OPENS | CLOSES |
|---|---|---|
| 1 | Jan. 1 | Mar. 31 |
| 2 | Apr. 1 | June 30 |
| 3 | Jul. 1 | Sep. 30 |
| 4 | Oct. 1 | Dec. 31 |

**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**

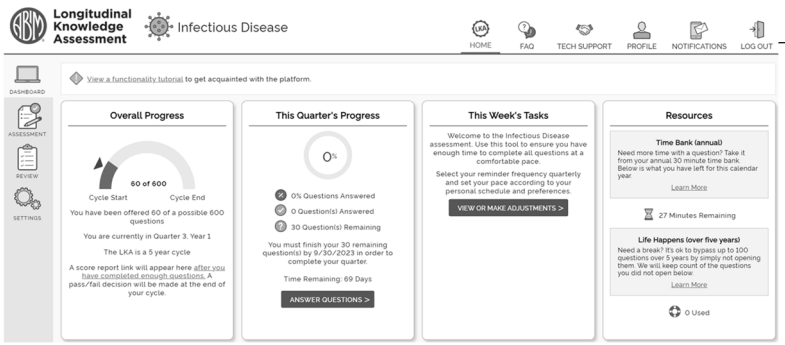
https://www.abim.org/maintenance-of-certification/assessment-information/infectious-disease

8

**OL1 How to Prepare for the Certification and Recertification, Including the LKA**

*Speaker: Helen Boucher, MD, FACP, FIDSA, (Hon) FRCPI*

©2026 Infectious Disease Board Review, LLC




**https://www.abim.org/maintenance-of-certification/assessment-information/assessment-options/longitudinal-knowledge-assessment/**

9

## Exam

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

10

## Exam

- **Little less than two minutes per question**
- **Unanswered questions 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**

11

## Breaks

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

**Note: Proctors monitor entire space (test room, locker rooms, reception)**

12


©2026 Infectious Disease Board Review, LLC

## Exam

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

13

## Exam

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

  ***And***

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

14

## Exam



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

15

## Disabled Test Takers

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

16



©2026 Infectious Disease Board Review, LLC

## Not allowed in test room (small storage locker provided)

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



17

## Questions about exam day

- Email: https://www.abim.org/contact.aspx
- Call ABIM 1-800-441-ABIM (2246)
  Mon-Fri: 8:30AM – 6PM

18

## Exam Tutorial

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

19

## Exam Format

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

- Questions ask about the work done (that is, tasks performed) by physicians in the course of practice:
  - Diagnosis/Testing - making a diagnosis/ordering and interpreting results of tests
  - Treatment/Care Decisions - recommending treatment or other patient care
  - Assessing risk, determining prognosis, and applying principles from epidemiologic studies
  - Understanding the underlying pathophysiology of disease and basic science knowledge applicable to patient care

20

**OL1 How to Prepare for the Certification and Recertification, Including the LKA**

*Speaker: Helen Boucher, MD, FACP, FIDSA, (Hon) FRCPI*

©2026 Infectious Disease Board Review, LLC

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

21

## Exam Content

- **Exam content determined by a pre-established blueprint**
- **Primary medical content categories are ….**

22

## 2019 ID Exam Blueprint

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

23

## Clinical Syndromes

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

24



©2026 Infectious Disease Board Review, LLC

## Clinical Syndromes (cont'd)

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

25

## Patient Populations

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

26

- **Note:**

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

**……..as an example**

27

## 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**

28



©2026 Infectious Disease Board Review, LLC

## Exam

- **Takes couple of years for new question to appear on exam and count. So, new developments in last 2 years less likely to be on exam and count**
  - **e.g. 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**

29

## 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% |
| 2025 | 390 | 93% |

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

30

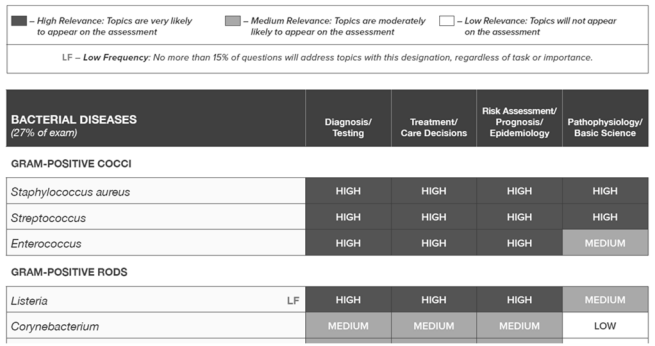
## How Blueprint Ratings are Used to Assemble the MOC Assessment?

- Blueprint reviewer provided ratings of relative frequency in practice and importance for each content topic
- Frequency and importance rated on a 3-point scale - low, medium, high
- Parameters for selecting MOC questions according to the ratings:
  - At least 70% of questions will address high-importance content (green)
  - No more than 30% of questions will address medium-importance content (yellow)
  - No exam questions will address low-importance content (red)
  - Independent of the importance and task ratings, no more than 15% of questions will address low-frequency content

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

31

## How is MOC Content Different?




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

32

**OL1 How to Prepare for the Certification and Recertification, Including the LKA**

*Speaker: Helen Boucher, MD, FACP, FIDSA, (Hon) FRCPI*

©2026 Infectious Disease Board Review, LLC

## 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

33

## 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.)

34

## What to do from now to exam

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

35

## Thank You: Jack Bennett & Bennett Lorber



Good Luck
To You All !

36

**OL1 How to Prepare for the Certification and Recertification, Including the LKA**

*Speaker: Helen Boucher, MD, FACP, FIDSA, (Hon) FRCPI*

©2026 Infectious Disease Board Review, LLC

## Questions, Comments?

- Helen.boucher@tuftsmedicine.org




Dr. Helen Boucher

37



©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

**OL2**

# Antimicrobial Toxicities II

**Douglas Black, PharmD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Antimicrobial Therapy II: More Toxicities and Pharmacologic Issues You Should Know

**Douglas Black, PharmD**
**University of Washington**

8/11/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- Editor, *The Sanford Guide to Antimicrobial Therapy*

## Case vignette #1

- A 22-yo woman presents with acute onset chest pain and painful swallowing that started 2 days ago.
- 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 acne vulgaris five days ago.
- Suspicion: drug-induced (pill) esophagitis.

## Based on the case, which antibacterial do you suspect she was taking?

a. Levofloxacin

b. Cephalexin

c. Linezolid

d. Metronidazole

e. Doxycycline



©2026 Infectious Disease Board Review, LLC

**Based on the case, which antibacterial do you suspect she was taking?**

a. Levofloxacin

b. Cephalexin

c. Linezolid

d. Metronidazole

e. Doxycycline

- **PILL ESOPHAGITIS**: Inflammation or ulceration of the esophageal mucosa caused by direct contact with a drug.
- Characterized by sudden onset odynophagia, retrosternal chest pain, dysphagia.
- Symptoms appear hours (even days) after drug ingestion.
- Risk factors:
  - Supine position after drug ingestion, inadequate water intake
  - Pre-existing esophageal motility disorder
  - Older age
  - Large or multiple medications
- Management:
  - Discontinue offending agent, hydration, soft diet
  - Supportive treatments: sucralfate, PPIs, viscous lidocaine

**Other antimicrobials associated with pill esophagitis**

- Azithromycin
- Clindamycin
- Penicillins (rare)
- Rifampin
- Tetracyclines (most common)
- TMP-SMX

## Case vignette #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 WNL
- Four days ago, began valacyclovir 1 gm q8h for shingles.



©2026 Infectious Disease Board Review, LLC

**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

**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

**(Val)acyclovir neurologic toxicity**

- Presentation
  - Early: agitation, hallucinations, confusion, disorientation
  - Later: tremor, myoclonus, delirium
  - Rare: seizures, extrapyramidal symptoms
- Risk factors: renal impairment, age, high doses, dehydration
- Pathophysiology: accumulation of CMMG (9-carboxymethoxymethylguanine)
- Management
  - Stop drug
  - Adjust dosage if therapy must continue
  - Hydration
  - Hemodialysis (extreme cases)

**Other antimicrobials associated with neurotoxicity**

- Beta-lactams (seizures, encephalopathy)
- Ethambutol (optic neuritis, peripheral neuropathy)
- Fluoroquinolones (confusion, seizures, peripheral neuropathy, exacerbation of myasthenia gravis)
- Isoniazid (peripheral neuropathy, encephalopathy, psychosis, seizures)
- Linezolid (peripheral neuropathy, optic neuropathy, serotonin syndrome)
- Metronidazole (peripheral/optic/autonomic neuropathy, encephalopathy)
- Nitrofurantoin (peripheral neuropathy)



©2026 Infectious Disease Board Review, LLC

## Case vignette #3

- A 52-yo man presents to the ED with an itchy rash, angioedema, and fever (T 39.2°C) that started 24 hours ago. The rash began as diffuse erythematous papules on his neck that spread down his torso to his arms and legs.
- 4 weeks ago, a planned 6-week course of vancomycin was begun after surgical debridement for right fifth digit osteomyelitis.
- The next day, the rash has spread to his palms and soles, and there is concern for impending airway compromise due to facial swelling. He is admitted to the ICU.
- Significant lab findings: eosinophils 2025 cells/μL, elevated IgE, atypical lymphocytes, evidence of AKI. AST/ALT WNL.
- Blood cultures, ANA, HIV, and HSV serologies negative. Skin biopsy shows spongiotic dermatitis with perivascular eosinophils.

**What is the antimicrobial agent most commonly associated with DRESS in the US?**

a. TMP-SMX

b. Minocycline

c. Fluconazole

d. Azithromycin

e. Vancomycin

**What is the antimicrobial agent most commonly associated with DRESS in the US?**

a. TMP-SMX

b. Minocycline

c. Fluconazole

d. Azithromycin

e. Vancomycin

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

- T-cell-mediated SCAR most commonly associated with ASMs, antibiotics, allopurinol, and NSAIDs.
- Delayed type IV hypersensitivity reaction.
- Typical latency: 2-6 weeks.
- Clinical presentation:
  - Rash, fever
  - Facial edema
  - Lymphadenopathy
  - Eosinophils >700 cells/μL, atypical lymphocytosis
  - Internal organ involvement
- RegiSCAR can be helpful
- Management:
  - Stop drug, supportive care
  - Corticosteroids



©2026 Infectious Disease Board Review, LLC

## Antimicrobials associated with DRESS

- Vancomycin
- TMP-SMX
- β-lactams: amoxicillin, ceftriaxone, piperacillin-tazobactam
- Tetracyclines: doxycycline, minocycline
- Clindamycin
- Nitrofurantoin
- Antitubercular drugs: INH, rifampin, PZA, ethambutol
- Antivirals: nevirapine
- Dapsone

## Case vignette #4

- A 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.
- PMH: 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
- Plan: surgical debridement, ceftriaxone 2 gm IV q24h + metronidazole 500 mg q8h x6 weeks.

## 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

## 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



©2026 Infectious Disease Board Review, LLC

## 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 neurotoxins (e.g., vincristine).
- Clinical features:
  - Symmetric distal sensory neuropathy
  - ± Mild weakness, gait imbalance
  - Rare: central toxicity (ataxia, encephalopathy)
- Management: stop drug, neuropathic pain meds, PT/OT for gait.
- As with other drugs, recovery is slow (weeks to months). Often reversible if recognized early. Prolonged exposure may mean incomplete recovery.

## Case vignette #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: hypertension, 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).
- Meds: valsartan, chlorthalidone.
- Decision to incise and drain the wound, then begin TMP-SMX 2 DS tablets q12h until he is afebrile x3-5 days.
- On the third day, the WBC and all VS are WNL (he is afebrile), but his SCr has increased to 1.6 mg/dL.

## 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 q12h)

e. Change to dicloxacillin (500 mg po q6h)

## 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 q12h)

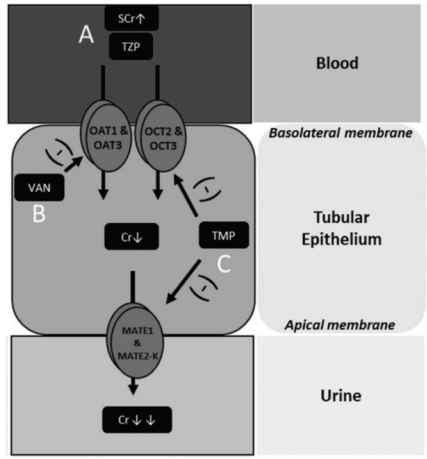
e. Change to dicloxacillin (500 mg po q6h)



©2026 Infectious Disease Board Review, LLC

**TMP-SMX-induced ↑SCr (without affecting glomerular filtration)**

- Trimethoprim can compete with creatinine for tubular secretion.
- Typical increase in SCr: around 20% (dose-dependent). Not expected 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)
- Also worth remembering: TMP-SMX can result in hyperkalemia.
  - TMP acts like amiloride, a K+ sparing diuretic.
  - More common at higher doses.




**How TMP increases SCr without affecting without affecting glomerular filtration**

## Case vignette #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 mentions his urine is dark brown.
- No fever, headache, myalgias, arthralgias, respiratory symptoms, abdominal pain, nausea, vomiting, diarrhea, anorexia, or weight loss.
- NKA, no 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, he finished a 14-day course of an antibiotic for a respiratory infection.

**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



©2026 Infectious Disease Board Review, LLC

**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

## Amoxicillin-clavulanate induced liver disease

- One of the most common causes of drug-induced liver disease (DILI). More common than amoxicillin alone.
- Risk factors: male sex, age >55, ethanol consumption, repeated use of the drug, other hepatotoxic drugs. Duration of treatment might be another risk factor.
- Average onset: 3 weeks after start 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 (might take 6 months).

## Other antimicrobials associated with drug-induced liver disease

- Antimycobacterials: INH, PZA, rifampin, bedaquiline
- Macrolides (especially erythromycin)
- Minocycline (autoimmune hepatitis)
- Oxacillin
- Terbinafine
- TMP-SMX
- Azole antifungals
- Nevirapine

## Case vignette #7

- 65-yo mildly obese man, renal transplant recipient. Anti-rejection regimen includes prednisone. Active lifestyle.
- Estimated CrCl is 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 3-4 days after starting levofloxacin. He is switched to TMP-SMX to finish up his therapy.
- AT still painful 4 days later. Prednisone dose increased.
- One month later, he loses his footing and slips, rupturing his left AT.



©2026 Infectious Disease Board Review, LLC

**Which fluoroquinolone is most associated with Achilles tendon rupture?**

a. Gemifloxacin

b. Ciprofloxacin

c. Levofloxacin

d. Moxifloxacin

e. Delafloxacin

**Which fluoroquinolone is most associated with Achilles tendon rupture?**

a. Gemifloxacin

b. Ciprofloxacin

c. Levofloxacin

d. Moxifloxacin

e. Delafloxacin

**Fluoroquinolones and tendon toxicity**

- FQs can cause 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 (there are theories).
- Statins do not seem to increase the risk.

[redacted]

| 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 |



©2026 Infectious Disease Board Review, LLC

## Management of FQ tendon injury

- 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 seek evaluation and possible transition to a non-FQ alternative drug.
- 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.

## Case vignette #8

- A 68-yo man (5'10", weight 110 kg) complains of fatigue, easy bruising, and gum bleeding.
- PMH: obesity, type 2 diabetes, hypertension, CKD, 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 3 weeks ago), metformin, lisinopril, and aspirin.
- VS WNL. Hemoglobin 9.1 g/dL, hematocrit 27%, WBC 2,100/μL, platelets 62,000/μL, reticulocytes low. B12, folate WNL.

## What 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

## What 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



©2026 Infectious Disease Board Review, LLC

**Linezolid-induced myelosuppression**

- A reversible pancytopenia (lack of blasts/dysplasia on smear or marrow biopsy).
- Risk factors
  - Treatment >14 days
  - Older age
  - Renal dysfunction
  - Concomitant marrow-toxic drugs
- Monitoring recommendation
  - Weekly CBC w/diff if treatment >14 days.
- Management
  - Stop drug, switch to alternative agent.
  - Monitor CBC. Heme consult if counts continue to decline or fail to recover.
  - Recovery expected within 1-2 weeks.

**Other antimicrobials associated with myelosuppression**

- Beta-lactams (e.g., nafcillin, piperacillin-tazobactam)
- Chloramphenicol
- Flucytosine
- Ganciclovir, valganciclovir
- Pyrimethamine
- TMP-SMX
- Zidovudine

## Case vignette #9

- A 63-yo man (73 kg, 5'11") is admitted with worsening back pain.
- PMH: type 2 diabetes.
- Allergy: ceftriaxone (urticaria).
- Blood cultures on admission: *E. faecalis*, pan-sensitive.
- SCr: 1.3 mg/dL (estimated CrCl 62 mL/min).
- TEE: mitral valve vegetation. MRI: L5/S1 vertebral osteomyelitis.
- Proposed treatment: ampicillin 2 gm IV q4h + gentamicin 70 mg IV q8h (both x6-8 weeks).

**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 not well-defined in this setting

d. Drug-induced ototoxicity

e. Use of ampicillin in someone with ceftriaxone allergy



©2026 Infectious Disease Board Review, LLC

**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 not well-defined in this setting

d. Drug-induced ototoxicity

e. Use of ampicillin in someone with ceftriaxone allergy

| 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

**Other antimicrobials associated with ototoxicity**

- Aminoglycosides
- Capreomycin
- Macrolides (especially erythromycin)
- Vancomycin

## Case vignette #10

- 53-yo man in the ED s/p seizure, loss of consciousness.
- PMH: alcohol abuse, seizure disorder. Renal function WNL.
- Seizures managed, empiric tx for meningitis (ceftriaxone 2 gm q12h, ampicillin 2 gm q4h, vancomycin 1 gm q12h, dex).
- Head CT, LP findings unremarkable. Blood, urine cultures negative. CxR: RLL opacity. Day 2: ceftriaxone continued, other drugs discontinued, azithromycin added (500 mg IV q24h).
- Day 7: patient jaundiced. T bili 5.8 mg/dL (↑ from 2.1), D bili 3.4 mg/dL (↑ from 0.7). Mild RUQ pain.
- RUQ ultrasound: biliary sludge and cholelithiasis, no evidence of cholecystitis.



©2026 Infectious Disease Board Review, LLC

**Which drug is the likely explanation for these observations?**

a. Azithromycin

b. Ceftriaxone

c. Vancomycin

d. Ampicillin

e. Dexamethasone

**Which drug is the likely explanation for these observations?**

a. Azithromycin

b. Ceftriaxone

c. Vancomycin

d. Ampicillin

e. Dexamethasone

**Ceftriaxone pseudocholelithiasis**

- Ceftriaxone is excreted in the bile in high concentrations (1000s of µg/mL).
- Gallstones consisting of a ceftriaxone-calcium complex (often referred to as biliary sludge) can form, typically around day 9 of treatment.
- Risk factors: high doses, prolonged therapy, dehydration, parenteral nutrition, hypercalcemia.
- May be more common in children. There may also be genetic factors.
- Presentation: RUQ tenderness, nausea.
- LFTs: typically a cholestatic pattern.
- Stopping the drug is usually enough.
- Resolution of sludge takes ≈2 weeks.

**Case vignette #11**

- A 58-year-old man presents to the ED 45 minutes after experiencing sudden-onset nausea, flushing, palpitations, and vomiting.
- These symptoms began 20 minutes after consuming 2 glasses of red wine.
- Two days ago, he was started on metronidazole 500 mg po q8h for suspected *C. difficile* colitis.
- No known drug allergies. He takes no other medications.



©2026 Infectious Disease Board Review, LLC

**Which of the following best explains this reaction?**

a. Metronidazole-induced serotonin syndrome

b. Type 1 hypersensitivity reaction to metronidazole

c. Acetaldehyde accumulation

d. Ethanol-induced inhibition of metronidazole metabolism

e. The mechanism of this reaction is disputed

**Which of the following best explains this reaction?**

a. Metronidazole-induced serotonin syndrome

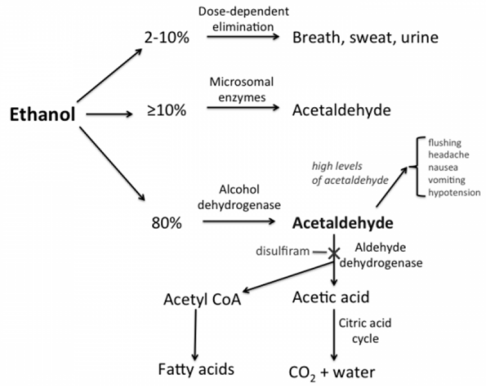
b. Type 1 hypersensitivity reaction to metronidazole

c. Acetaldehyde accumulation

d. Ethanol-induced inhibition of metronidazole metabolism

e. The mechanism of this reaction is disputed

**Ethanol Metabolism**









©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL3

# HIV-Associated Opportunistic Infections III

**Rajesh Gandhi, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# 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

8/11/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## HIV Associated Opportunistic Infections: Part 3

**Mucocutaneous Infections: Candida, VZV, HSV, EBV**

**Endemic Mycoses**

**Gastrointestinal (GI) Complications**

## Mucocutaneous Candidiasis in PWH

- Oropharyngeal and esophageal candidiasis common in people with HIV (PWH) who have CD4 counts <200
  - Esophageal candidiasis typically occurs at lower CD4 counts than oropharyngeal candidiasis
- Most *Candida albicans*
- Invasive candidiasis **NOT** HIV related
  - Candida in blood should raise suspicion of catheter related blood stream infection or injection drug use



©2026 Infectious Disease Board Review, LLC

## Oropharyngeal Candidiasis

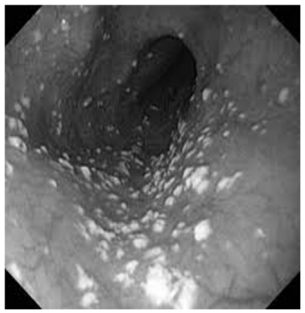
**Pseudomembranous** **Erythematous** **Angular cheilosis**



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

## Esophageal Candidiasis

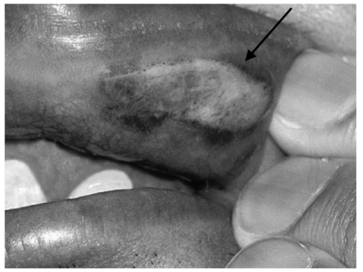


## Mucocutaneous Candidiasis in PWH: Management

- 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

## 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


©2026 Infectious Disease Board Review, LLC

## Causes of Odynophagia in People with Advanced HIV

- Esophageal candidiasis
- Giant aphthous ulcers
- HSV esophagitis
- CMV esophagitis

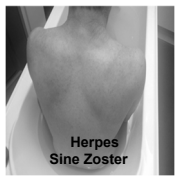
## Herpes Zoster

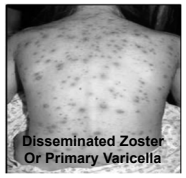
- **Pre ART**
  - 15-fold higher incidence of zoster than general population!
- **Post ART**
  - Still increased risk even on suppressive ART
- **Localized (dermatomal)**
  - May occur at all CD4 counts
    - More frequent when CD4 count <200 or HIV RNA not suppressed
  - Risk of zoster increased soon after ART initiation, possibly because of immune reconstitution inflammatory syndrome

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

## Localized and Disseminated Herpes Zoster



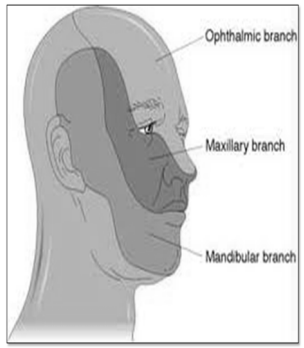







## Zoster Ophthalmicus
### Ophthalmic Branch CN V



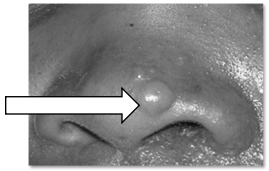




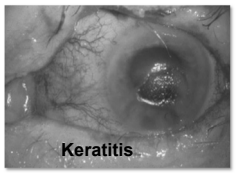
©2026 Infectious Disease Board Review, LLC

## Hutchinson's Sign As Precursor to VZV Eye Disease

(Nasociliary Nerve of Ophthalmic Branch CN V)







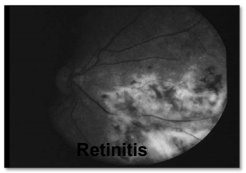




Image C. Stephen Foster, MD, Massachusetts Eye Research and Surgery Institute

- **Vesicles on tip of nose**, or vesicles on side of nose
- Accompanies development of ocular manifestations: keratitis, anterior uveitis

## Zoster Ophthalmicus Related Stroke

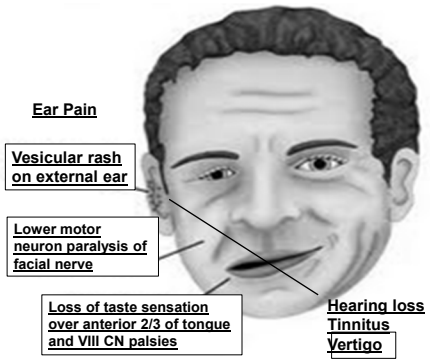
- Vascular inflammation and occlusion
- Days or months post zoster (median 4 months)
- Occasionally cutaneous lesions absent (33%)
- Diagnosis: PCR of CSF or VZV antibody production in CSF



Fugate JE, January 2020, Practical Neurology

## Ramsay-Hunt Syndrome: Herpes Zoster Oticus

**Geniculate Ganglion of Cranial Nerve VII**
**External Ear Vesicles and Facial Nerve Paralysis**




## Prevention of Zoster

- Recombinant VZV glycoprotein E /adjuvant AS01B (RZV-Shingrix)
- Recommended in adults with HIV aged ≥18 years, regardless of CD4 count
- 2-dose series at 0 and then at 2 to 6 months
- RZV should not be given during acute episode of herpes zoster

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

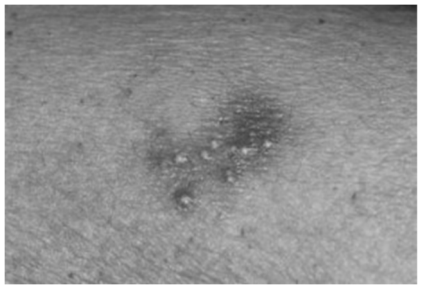


©2026 Infectious Disease Board Review, LLC

## Herpes Simplex Virus (HSV)

- **Orolabial herpes:** most common manifestation of HSV-1 infection
- **Genital herpes:** typically, HSV-2; increasingly HSV-1
  - Recurrences, viral shedding less often with genital HSV-1
- **Proctitis** in men who have sex with men
  - May not have external anal ulcers
- Other manifestations in PWH who have low CD4 counts (<100)
  - Esophagitis
  - Retinitis (acute retinal necrosis)
  - Chronic, extensive, deep genital ulcers, often acyclovir resistant
- Dissemination: rare, even in severely immunosuppressed patients

## Localized Herpes Simplex



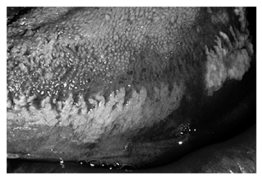
## Chronic Extensive Perirectal HSV in PWH with Low CD4 Count

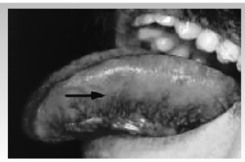


- Look for Acyclovir (ACV) Resistance with Viral Culture and Phenotypic Testing
- Treatment for ACV-resistant HSV: iv foscarnet; investigational drug: pritelivir

## Oral Hairy Leukoplakia EBV Associated









©2026 Infectious Disease Board Review, LLC

## 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

## HIV Diseases Associated with EBV

- Oral Hairy Leukoplakia
- Primary CNS Lymphoma

## Dermatologic Findings in PWH

**Prurigo nodularis**



Image courtesy of Dr. Anisa Mosam

**Kaposi Sarcoma (HHV-8 associated)**




www.idimages.org

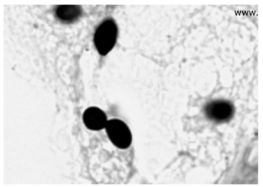
## HIV Associated Opportunistic Conditions: Part 3

**Endemic Mycoses**

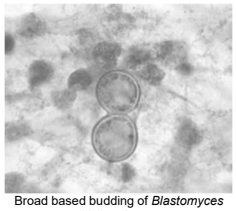

©2026 Infectious Disease Board Review, LLC

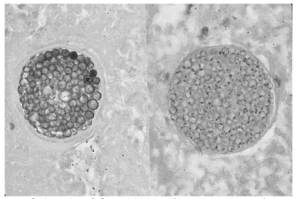
## Other Fungal Diseases that are Covered Elsewhere in IDBR

- Look for questions on patients with HIV and….



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)

www.idimages.org

## *Talaromyces marneffei* (formerly *Penicillium marneffei*)

- Dimorphic fungus: SE Asia, East Asia, South Asia
- Advanced HIV: risk factor for severe disease
- Skin lesions: central-necrotic or umbilicated papules
- Pulmonary, GI involvement; hepatosplenomegaly

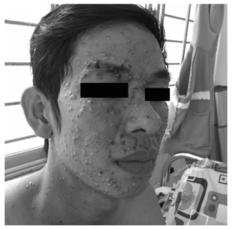


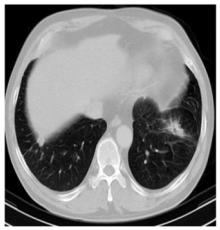


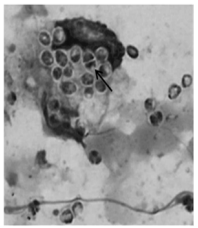


https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/talaromycosis?view=full

## *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

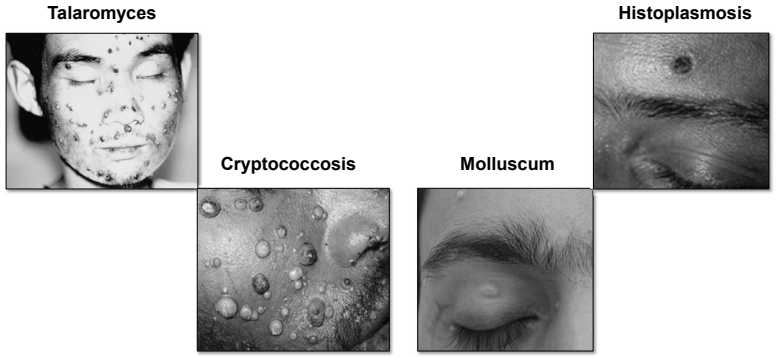
## Talaromycosis: Primary Prophylaxis

- **Indications**
  - CD4 count <100 and not taking ART or treatment failure who either:
    - Reside in hyperendemic regions in Northern Thailand, Vietnam, southern China
    - Traveler to hyperendemic areas
- **Preferred: Itraconazole 200 mg daily**
- **Alternative: Fluconazole 400 mg once weekly**

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


©2026 Infectious Disease Board Review, LLC

## Skin Lesions for HIV Associated Endemic Mycoses May Be Difficult to Distinguish




## GI Complications

## 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

## 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


©2026 Infectious Disease Board Review, LLC

## 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

## 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

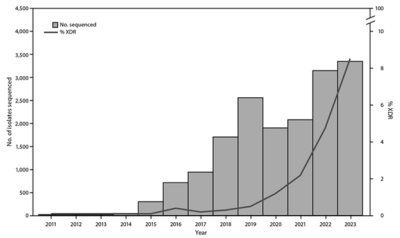
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/bacterial-enteric?view=full

U.S. Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Weekly / Vol. 75 / No. 13 April 9, 2026

Emergence of Extensively Drug-Resistant Shigellosis — United States, 2011–2023

**April 29, 2026**

- 8.5% of Shigella now XDR: resistant to azithromycin, ampicillin, ciprofloxacin, ceftriaxone, TMP/SMX
  - 1/3 *Shigella flexneri*
- 38% hospitalized; no deaths
- Risk factors from previous studies: Men who have sex with men, people experiencing homelessness, people with HIV




- No current treatment recommendations
  - Pivmecillinam, fosfomycin and oral carbapenems (e.g., sulopenem) might be effective; not approved for shigellosis.

## Thank you


©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL4

# Statistics

**Khalil Ghanem, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

## Online Only Lectures

---

# OL5

# Review of Basics:
# HIV

**Roy Gulick, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# HIV/AIDS 2026



**Roy M. Gulick, MD, MPH**
**Chief, Division of Infectious Diseases**
**Rochelle Belfer Professor in Medicine**
**Associate Dean for Clinical Research**
**Weill Cornell Medicine**
**New York City**

Weill Cornell Medicine
NewYork-Presbyterian

## Disclosures

- No pharmaceutical or device company relationships.
- Co-Chair, U.S. DHHS Adult and Adolescent ART Treatment Guidelines Panel

## ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
- Pathogenesis (<2%)
- Lab testing (<2%)
- HIV Treatment Regimens (4.5%)
- Opportunistic Infections (5%)
- Malignancies (<2%)
- Other complications of HIV (2%)
- Related issues (<2%)

## Morbidity and Mortality Weekly Report (MMWR): 1981

1981 June 5;30:250–2

*Pneumocystis* Pneumonia – Los Angeles

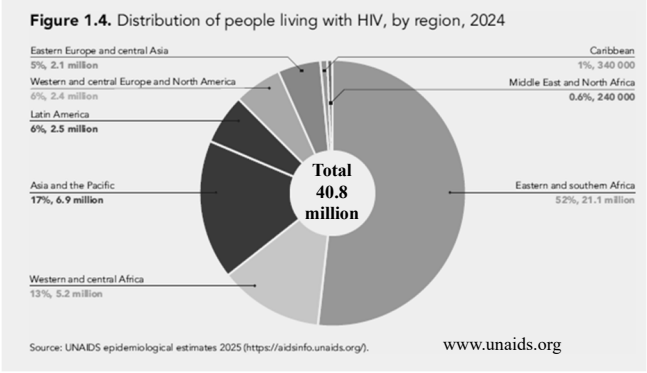
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

**2024: >88 million people infected globally; over 1/2 have died**

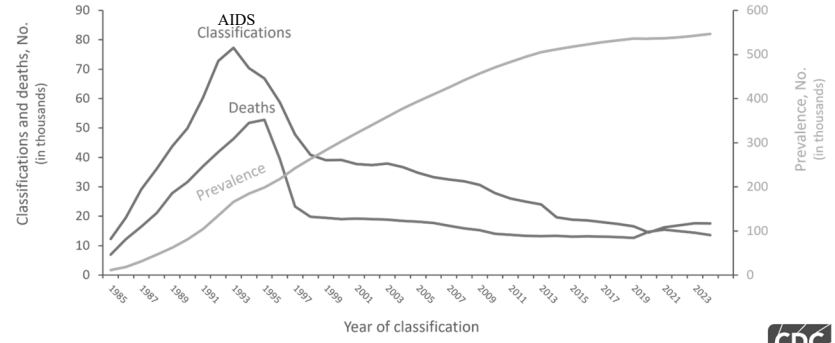


©2026 Infectious Disease Board Review, LLC

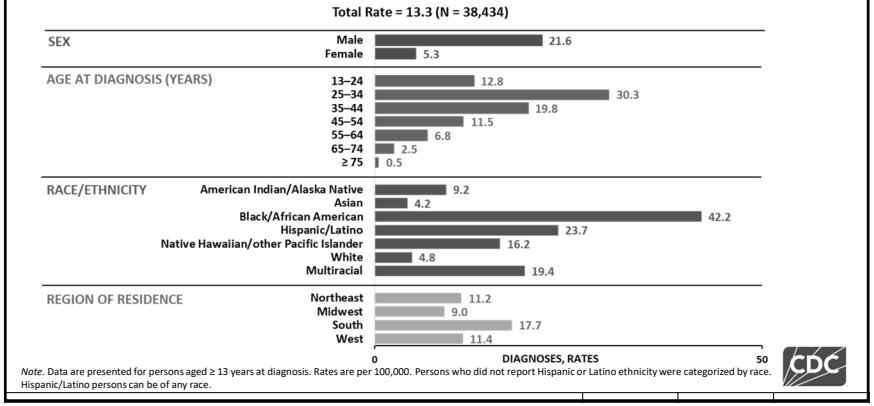
# People with HIV (PWH): Global



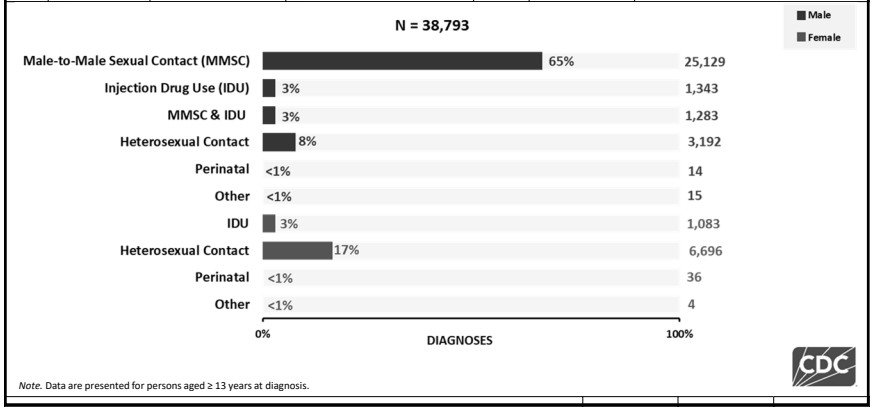

# AIDS, Deaths, and Prevalence 1985–2024 — US and 6 Dependent Areas




# HIV diagnoses rates, by selected characteristics, 2024—United States



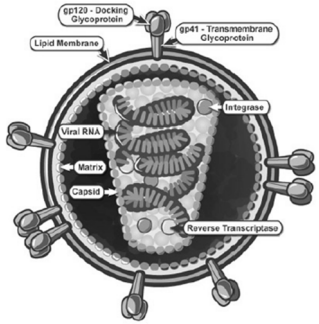

# HIV diagnoses, by transmission category and sex, 2024—United States and 7 territories and freely associated states






©2026 Infectious Disease Board Review, LLC

## Human Immunodeficiency Virus (HIV)




- formerly HTLV-III; isolated 1983-4
- human retrovirus – outer glycoprotein coat, inner protein coat and genetic material: RNA (2 strands)
- types: HIV-1 and HIV-2
- subtypes (clades): B most common in North America and Europe
- zoonosis from primates (~1900)
- target cell: CD4+ T-lymphocyte

## Question 1

Which is the current sequence of initial and confirmatory HIV diagnostic testing?

A. ELISA, followed by Western Blot
B. ELISA, followed by HIV RNA
C. ELISA, followed by immunoassay
D. HIV RNA, followed by Western Blot
E. HIV RNA, followed by ELISA
F. HIV RNA, followed by immunoassay

## 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

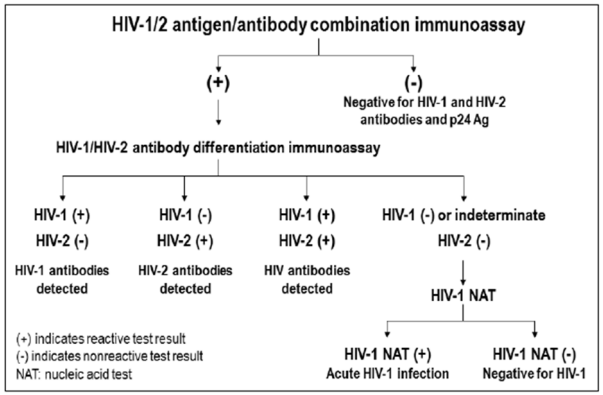
## HIV Testing

- 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 available
- HIV viral testing (direct)
  - p24 antigen
  - viral culture
  - HIV RNA (viral load)
- Combination antibody + antigen test
  - window period ↓ 3 months → 2 weeks



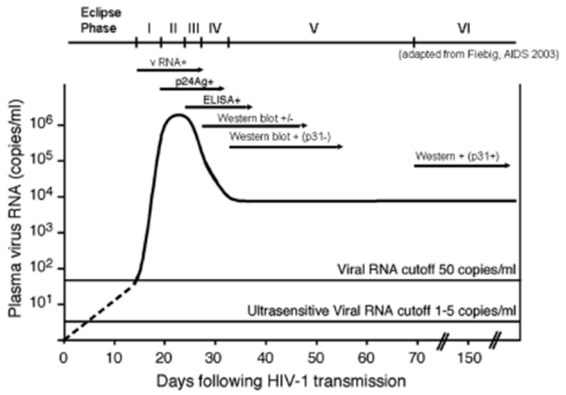
©2026 Infectious Disease Board Review, LLC

Recommended Laboratory HIV Testing Algorithm for Serum or Plasma Specimens




CDC 2014

Natural History and Laboratory Staging of HIV Infection




Cohen JID 2010;202:S270

# Question 2

Who should NOT be routinely offered HIV testing?

A. 32-year-old pregnant woman in a stable relationship
B. 23-year-old sexually active monogamous gay man
C. 75-year-old former injection drug user
D. 10-year-old pre-pubescent girl
E. All of them should be routinely offered HIV testing


# 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





©2026 Infectious Disease Board Review, LLC

## U.S. Preventive Services Task Force (UPSTF)

Recommendations

- Screen adolescents and adults ages 15 to 65 for HIV infection.
- Screen all pregnant women.
- Younger adolescents and older adults who are at increased risk should also be screened.
- This is a grade A recommendation ("high certainty that the net benefit is substantial").
- Federal Rule: Private Insurance and Medicare must offer A or B services without a co-pay.

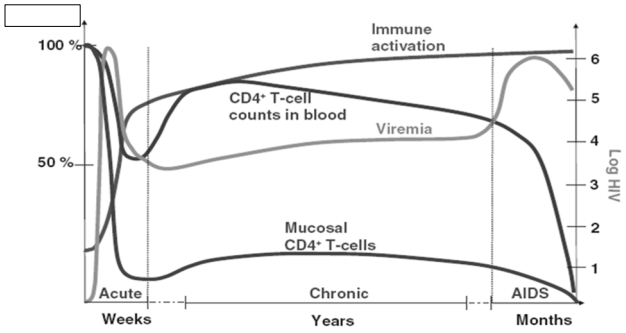
Ann Intern Med 2013;159:1-36

## HIV Transmission Risks

| Exposure from HIV+ source | Risk per exposure (%) | Risk per exposure (number) |
|---|---|---|
| Blood transfusion | 93% | 9/10 |
| Needle-sharing injection drug use | 0.6% | 1/167 |
| Percutaneous needle stick | 0.2% | 1/500 |
| Receptive anal sex | 1.4% | 1/70 |
| Insertive anal sex | 0.1% | 1/1000 |
| Receptive penile-vaginal sex | 0.08% | 1/1250 |
| Insertive penile-vaginal sex | 0.04% | 1/2500 |
| Oral sex | low | very low |
| Mother-to-child | 23% | 1/4 |

Patel AIDS 2014;28:1509

## Time Course of HIV Infection




Grossman Nature Medicine 2006;12:289-295

## CDC Adult AIDS Case Definition

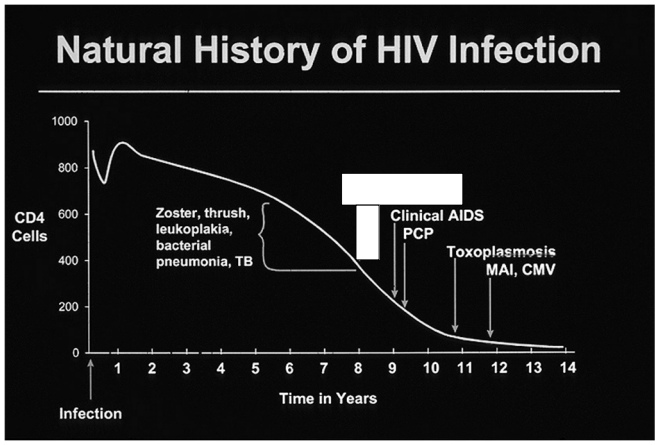
- 1982: "AIDS" -- list of diseases (definitive diagnosis) and disqualifying conditions
- 1985: HIV antibody testing added to definition
- 1987: presumptive diagnoses with a positive HIV antibody added
- 1993: CD4 <200 (without symptoms) and other diagnoses added



©2026 Infectious Disease Board Review, LLC

## 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: Pneumocystis, Cryptococcus, Histoplasma
  - Viral: CMV
  - Parasitic: Toxoplasma
  - Malignancies: Kaposi's sarcoma, Non-Hodgkin's-lymphoma




## Goal of Antiretroviral Therapy

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

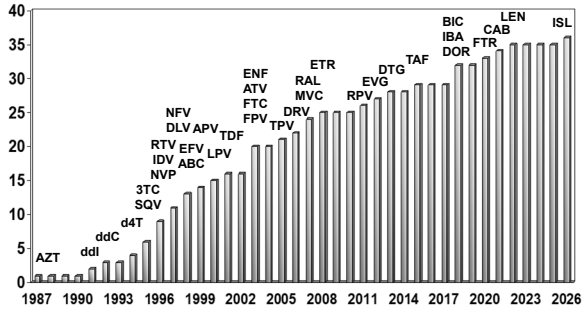
## When to start ART?

| Guidelines | AIDS/ symp-toms | CD4 <200 | CD4 200-350 | CD4 350-500 | CD4 >500 |
|---|---|---|---|---|---|
| | | ←asymptomatic→ | | | |
| **US DHHS '25** www.clinicalinfo.hiv.gov | treat | treat | treat | treat | treat |
| **IAS-USA '24** JAMA 2025;333:609-628 | treat | treat | treat | treat | treat |

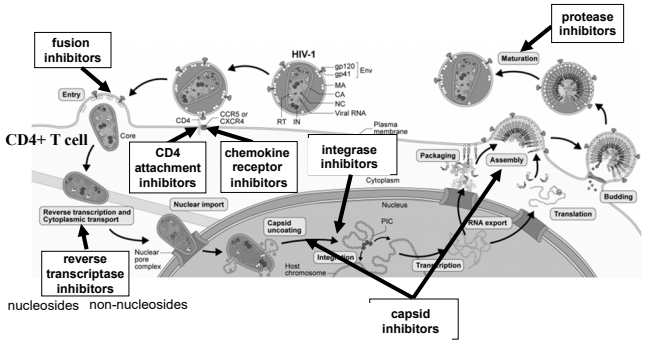
U.S. DHHS HIV Treatment Guidelines:
- ART is recommended for all persons with HIV to ↓ morbidity and mortality **(AI)** and to prevent transmission of HIV to others **(AI)**.
- Initiate ART immediately (or as soon as possible) after HIV diagnosis.


©2026 Infectious Disease Board Review, LLC

## Antiretroviral Drug Approval: 1987 - 2026




## Life Cycle of HIV




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

## Approved ART: 2026*

**nucleoside/tide RTIs (NRTIs)**
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- islatravir (ISL)
- 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)

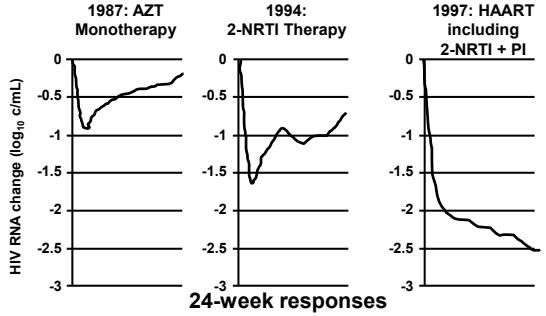
**integrase inhibitors (IIs)**
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

**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, SQV, IDV, APV, FPV, + ENF (T-20) discontinued

## Antiretroviral Activity: 1987-1997




Fischl, *NEJM* 1987
Eron, *NEJM* 1995
Hammer, *NEJM* 1996
Gulick, *NEJM* 1997
Cameron, *Lancet* 1998



©2026 Infectious Disease Board Review, LLC

## Question 3

Which class of ART is recommended as the basis 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

## Question 3

Which class of ART is recommended as the basis 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

## What to start?

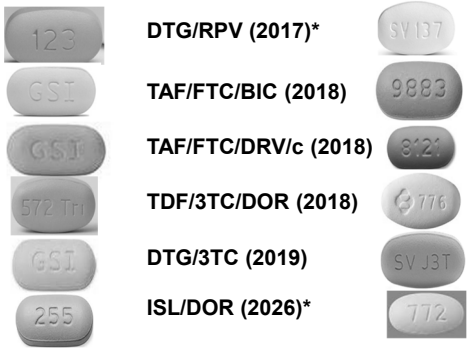
### Recommended regimens:

| 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 9/25

## Approved Single-Tablet ART Regimens




*FDA approved only for maintenance therapy



©2026 Infectious Disease Board Review, LLC

## Cabotegravir (CAB)

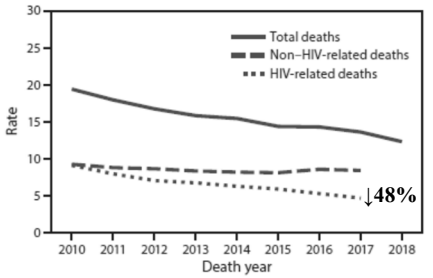


- Integrase inhibitor similar to dolutegravir
- Nanotechnology formulation; injectable
- Phase 3 studies of IM CAB/IM rilpivirine (RPV) for treatment switch demonstrated non-inferiority to standard oral treatment regimens
  - Orkin NEJM 2020;382:1124
  - Swindells NEJM 2020;382:1112
- U.S. FDA approved 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

## U.S. HIV Deaths: 2010-2018

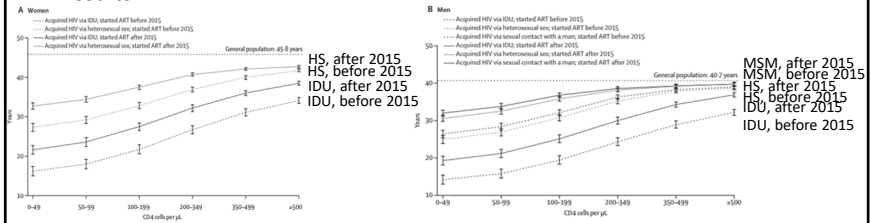
**FIGURE 1. Age-adjusted rates* of total deaths,† human immunodeficiency virus (HIV)–related deaths,§ and non–HIV-related deaths among persons aged ≥13 years with diagnosed HIV infection — United States, 2010–2018¶**




Bosh, MMWR 2020;69:1717-24

## 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

## HIV Prevention Strategies

**A**bstain, **B**e faithful, **C**ondoms,
**C**ounseling & 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

Female-controlled microbicides ✗
☑ Abdool Karim Science 2010
Marrazzo NEJM 2015
Delany-Moretlwe Lancet ID 2018

☑ 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
Molina NEJM 2015
McCormack Lancet 2016
Landovitz NEJM 2021
Bekker NEJM 2024
Kelley NEJM 2025

**OL5 Review of Basics: HIV/AIDS**
*Speaker: Roy Gulick, MD, MPH*

©2026 Infectious Disease Board Review, LLC

## 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


## 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


## 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
  -  = IM CAB or SQ LEN

FDA PrEP approvals:

- 2012: TDF/FTC
- 2019: TAF/FTC (men only)
- 2021: injectable cabotegravir (CAB)
- 2025: subcutaneous lenacapavir (LEN)

## Recent PrEP Studies

| Study (reference) | Study population (without HIV) | Design | Results: Reduction in HIV Infection with PrEP |
|---|---|---|---|
| **PROUD** McCormack Lancet 2015;387:54-60 | 544 MSM in UK | TDF/FTC (daily) immediate vs. delayed | ↓86%  |
| **HPTN 083** Landovitz NEJM 2021;385:595 | 4566 MSM and TGW globally | TDF/FTC (daily) vs. IM CAB every 2 months | IM CAB: ↓66% vs. TDF/FTC  |
| **PURPOSE 1** Bekker NEJM 2024;391:1179 | 5338 young women in South Africa and Uganda | TDF/FTC or TAF/FTC (daily oral) vs. SQ LEN every 6 months | SQ LEN: 0 infections!  |

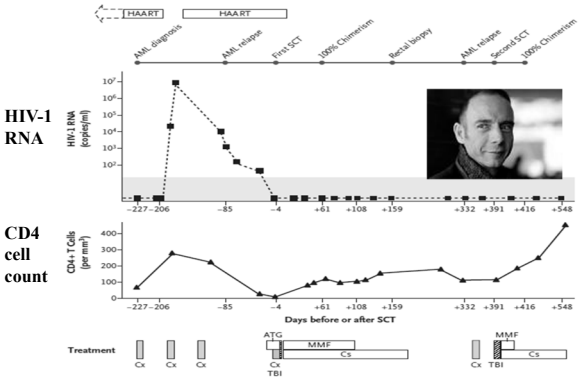



©2026 Infectious Disease Board Review, LLC

## HIV Vaccine Studies

| HIV Vaccine | N | Approach | Response | Result |
|---|---|---|---|---|
| **AIDSVAX** Pitisuttithum JID 2006 | 2546 | gp120 subunit | antibody | no effect |
| **STEP** Buchbinder Lancet 2008 | 3000 | Adenovirus vector + HIV genes | CTL | no effect |
| **RV144** Rerks-Ngarm NEJM 2009 | 16,402 | Canarypox vector + HIV genes + boost with gp120 | both | **31%** ↓ in HIV |
| **HVTN 505** Hammer NEJM 2013 | 2504 | DNA prime + adenovirus boost | CTL | futility |
| **HVTN 702** Gray NEJM 2021 | 5404 | ALVAC-HIV + bivalent sub C gp120 | both | no effect |
| **HVTN 705** Gray Lancet ID 2024 | 2637 | Ad26.Mos4.HIV + mosaic GAG/POL /ENV Ag+ C gp140 | both | no effect |
| **HVTN 706 Mosaico** Buchbinder Lancet HIV 2025 | 3900 | Mosaic adenovirus vector+ mix of soluble proteins | both | no effect |

## HIV Cure (N=4) 10+!




Hutter NEJM 2009;360:692

**Cure #2** *first Latino
London
Gupta, Nature 2019;568:244
**Cure #3** *first woman
NYC
Hsu, Cell 2023;186:1115
**Cure #4**
Dusseldorf
Jensen, Nat Med 2023;29:583
**Cure #5**
City of Hope
Dickter, NEJM 2024;390:669
**Cure #6** *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544
**Cure #7** *first Δ32 hetero donor
Berlin
Gaebler, Nature 2026;650:701
**Cure #8** *HIV rebound
Chicago
Rubinstein CROI 2025 #531
**Cure #9**
Oslo
Myhre Nat Micro 2026;11:1374
+ more!

## 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.


## 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


**OL5 Review of Basics: HIV/AIDS**
*Speaker: Roy Gulick, MD, MPH*


©2026 Infectious Disease Board Review, LLC

**Online Only Lectures**

---

**OL6**

# Review of Basics: Transplant Infectious Disease

**Camille Kotton, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Review of Basics: Transplant Infectious Disease

**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; Secretary, The Transplantation Society

8/11/2026




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

| Company | Role | Details |
|---|---|---|
| Evrys | Consultant | CMV treatment in transplant |
| Merck | Consultant, Adjudication committee member, Data monitoring committee, symposium speaker (CME) | Transplant infections<br>CMV antiviral trial, adjudication<br>Pneumococcal vaccine, adjudication |
| 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 |

## 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/review to subsequent similar talks**

**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) |



©2026 Infectious Disease Board Review, LLC

## 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

## 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<br>• Graft versus host disease, grade 3 or 4<br>• Hematological malignancy on therapy<br>• Lung transplant<br>• Fewer than 1% peripheral B-cells assessed in past 6 months | • B-cell depleting agents in past 12 months (eg, rituximab, ofatumumab, ocrelizumab, others)<br>• CAR-T therapy in past 12 months<br>• Abatacept |
| Moderate risk immunocompromised patients | • Solid organ transplant other than lung<br>• Solid tumor on treatment<br>• Congenital agammaglobulinemia<br>• Graft versus host disease, grade 1 or 2<br>• HIV infection with CD4 <200 cells/mm$^3$<br>• Other severe primary immunodeficiency | • Tyrosine kinase inhibitor (eg, ibrutinib, acalabrutinib, others)<br>• High-dose corticosteroids (>20 mg prednisone or equivalent for >4 wks)<br>• Anthracycline derivates |
| Lower risk immunocompromised patients | • HIV infection with CD4 >200 cells/mm$^3$<br>• Inflammatory bowel disease<br>• Cirrhosis<br>• ESRD<br>• Solid tumor (treatment >12 months prior) | • Anti-TNF<br>• Anti-IL-6<br>• Anti-IL-12 and -23<br>• Corticosteroids ≤10 mg long-term, or <20 mg for <4 wks<br>• 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

## 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://www.cdc.gov/yellow-book/hcp/travelers-with-additional-considerations/immunocompromised-travelers.html (28 April 2026)



***"Net state of immunosuppression"***
**Dr. Robert Rubin, Massachusetts General Hospital**

**IMMUNOSUPPRESSION IS 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
  - Induction agents @ time of transplant
  - Chronic immunosuppression
  - Treatment of rejection


©2026 Infectious Disease Board Review, LLC

## 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

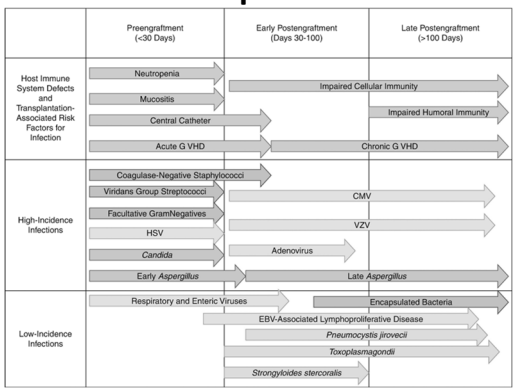
## HCTs performed in United States, 2019-2023
## Center for International Blood and Marrow Transplant Research

| Donor type | No. | % |
|---|---|---|
| Autologous stem cell | 66,418 | 58 |
| Allogenic stem cell | 47,499 | 42 |
| HLA-matched sibling | 9,319 | 8 |
| Other related donor | 11,535 | 10 |
| Unrelated | 26,645 | 23 |
| Grand Total | 113,917 | 100 |

https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report#summary accessed 22 March 2026

10

## 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)

## 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

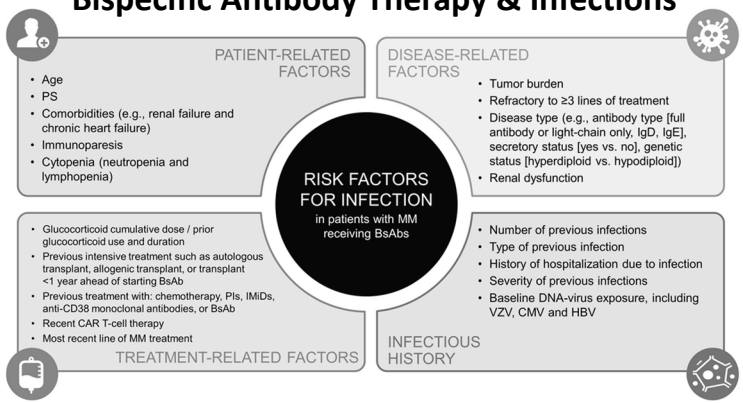

©2026 Infectious Disease Board Review, LLC

## 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

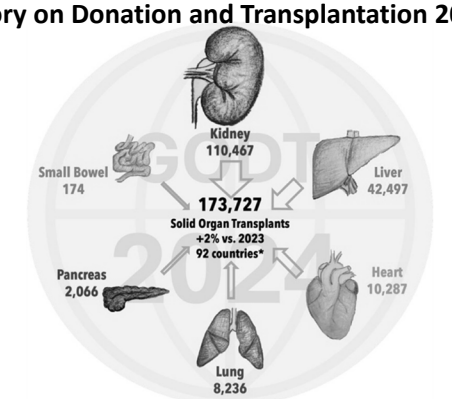
Stewart AG and Henden AS, Infectious complications of CAR T-cell therapy: a clinical update. Ther Adv Infect Dis. 2021.
*Kampouri E et al, CMV Reactivation and CMV-Specific Cell-Mediated Immunity after Chimeric Antigen Receptor T-Cell Therapy , CID 2023

## 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

## Organ Donation and Transplantation Worldwide: The Global Observatory on Donation and Transplantation 2024 Report




* Data submissions included until October 31, 2025.

Martin, Friederike; Carmona, Mar; Mahillo, Beatriz; Alvarez, Marina; Luengo, Amparo; Chatzixiros, Efstratios; López-Fraga, Marta; Dominguez-Gil, Beatriz; Tullius, Stefan G. Transplantation, March 2026,110(3):e655-e669

## National Organ Transplant Data – USA

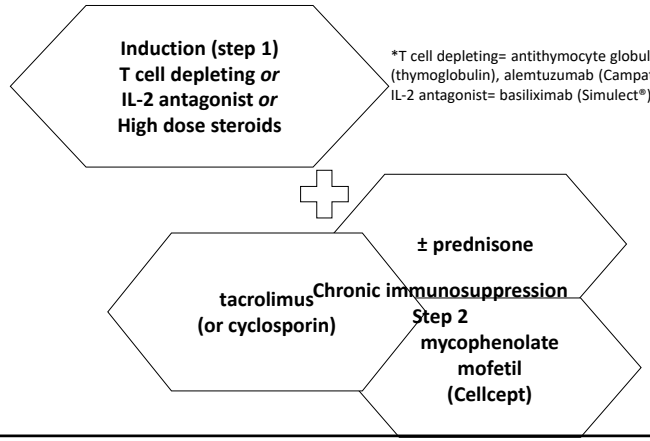
> 1 million transplants done in USA since 1988

| | To Date | 2026 | 2025 | 2024 | 2023 | 2022 | 2021 | 2020 | 2019 |
|---|---|---|---|---|---|---|---|---|---|
| All Organs | 1,072,835 | 7,903 | 49,065 | 48,150 | 46,634 | 42,889 | 41,356 | 39,036 | 39,719 |
| Kidney | 629,830 | 4,416 | 27,574 | 27,760 | 27,332 | 25,500 | 24,670 | 22,817 | 23,401 |
| Liver | 237,334 | 2,133 | 12,344 | 11,458 | 10,659 | 9,528 | 9,236 | 8,906 | 8,896 |
| Pancreas | 9,614 | 11 | 107 | 114 | 102 | 108 | 143 | 135 | 143 |
| Kidney / Pancreas | 29,530 | 106 | 804 | 733 | 812 | 810 | 820 | 827 | 872 |
| Heart | 101,865 | 670 | 4,587 | 4,572 | 4,545 | 4,111 | 3,818 | 3,658 | 3,552 |
| Lung | 59,214 | 557 | 3,490 | 3,340 | 3,026 | 2,692 | 2,524 | 2,539 | 2,714 |
| Heart / Lung | 1,641 | 3 | 61 | 64 | 54 | 51 | 45 | 58 | 45 |
| Intestine | 3,651 | 3 | 88 | 97 | 95 | 82 | 96 | 91 | 81 |

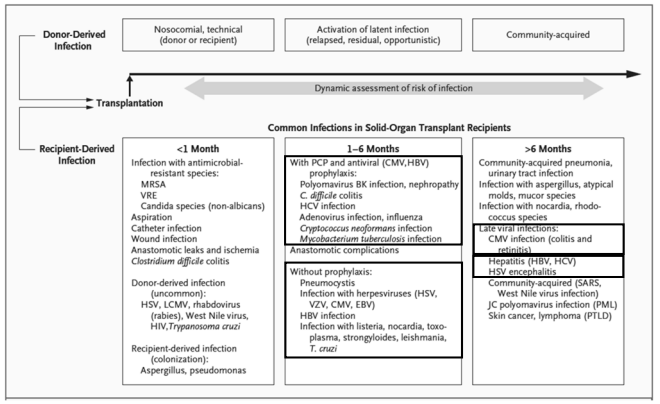
*UNOS data downloaded 14 March 2026
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/


©2026 Infectious Disease Board Review, LLC

## Common Immunosuppression after Organ Transplant




## Timeline of Infection after Organ Transplantation



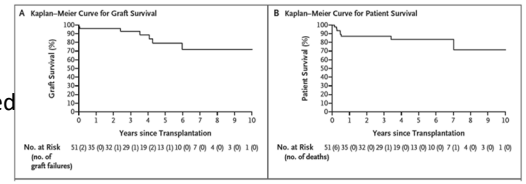

Fishman, Infection in Solid-Organ Transplant Recipients, NEJM 2007

## 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 standard of care
- Need to have a good plan for medications (insurance)
- Trend towards shorter treatment protocols

## Longer-Term Outcomes of *HIV-Positive–to–HIV-Positive Renal Transplantation*, Selhorst, Muller et al, NEJM 2018

- n=51
- 8 patients (16%) died after transplantation from non–graft-related causes
- No transmission of drug resistant virus




- **5-year overall survival and graft survival similar to the 3-year overall survival and graft survival observed among HIV-positive patients who received an organ from an HIV-negative donor in the United States**


©2026 Infectious Disease Board Review, LLC

## 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

## 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 to prevent illness
- Management: peritransplant/initiation of immunomodulatory tx
- Prophylaxis and/or screening after transplant/immunomodulatory therapy started

Pearl:
pre-immunosuppression vaccination optimizes vaccine immunogenicity

Best (only?) time to give MMR, varicella, yellow fever vaccines



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 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, 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 PCV21 (pneumococcal), Tdap, influenza vaccine, Shingrix x 2 (shingles)


©2026 Infectious Disease Board Review, LLC

Review for Infectious Disease Exposures/Risk Factors
*(my dot phrase)*

- Birth place: ***
- Have they lived outside of New England? ***
- Have they lived outside of the country for more than 3 months? ***
- Have they ever lived in the American Southwest, Arizona, New Mexico, California? *** (Coccidioides/Valley Fever risk)
- Any exotic travel history, outside of Europe, Canada, Australia (i.e. Asia, Africa, South or Central America)? Where/how long? ***
- Are they planning to travel to any exotic regions after transplant? If yes, where? ***
- Served in the military abroad? ***
- Who do they live with currently, or live alone? ***
- Wellwater - *** *(If yes, we discussed the recommendation to boil water or drink bottled water after transplant, filters not adequate)*
- Do they use a Nettie pot or other similar device to lavage to their sinuses; if so do they use untreated water? (chlorinated tap water should be fine) ***
- Do they eat any raw meat, raw milk/dairy, raw fish, raw seafood? ***
- Do they eat cold cuts? *** (Given the risk of Listeria and other pathogens we would discourage this after transplant)
- Employment/career: ***
- Any hobbies that involve exposure to outdoors/woods, gardening/farming, animals etc? ***
- Any pets at home or animal contacts? *** (*We discourage exposure to birds, reptiles, rodents after transplant due to zoonotic risk. Horses convey a risk of Rhodococcus equi. Dogs, cats, and fish are fine, although we discourage changing the kitty litter due to the risk of Toxoplasmosis, and discourage cleaning the fish tank due to the risk of mycobacterial and other infections)*
- Have they seen a dentist in the past year? *** Any dental issues? ***
- Have they ever been on a long course of antibiotics (>3 weeks) or intravenous antibiotics at home? ***

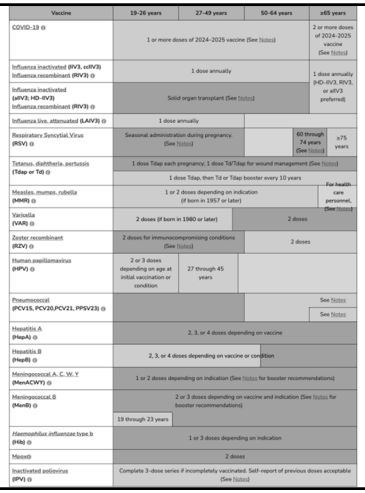
## Pre-Solid Organ Transplant Evaluation (MGH)

| | 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 |

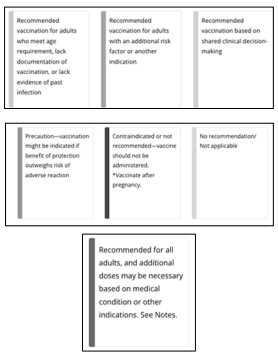
## USA Adult Immunization Schedule by Age, ≥ 19yo, 2025



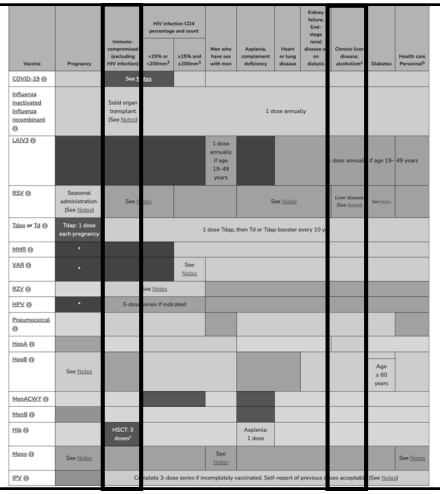

https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-age.html




## USA Adult Immunization Schedule by Condition, ≥19yo, 2025



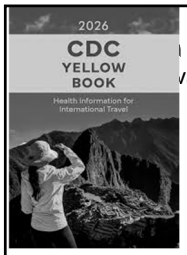

https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-medical-condition.html




**OL6 Review of Basics: Transplant Infectious Disease**

*Speaker: Camille Kotton, MD, FAST, FIDSA*

©2026 Infectious Disease Board Review, LLC




of immunocompromised
vaccines

CDC YELLOW BOOK
Immunocompromised Travelers
CDC Yellow Book 2026
Travelers with Additional Considerations
Author(s): Camille Kotton, Andrew Kroger, David Freedman

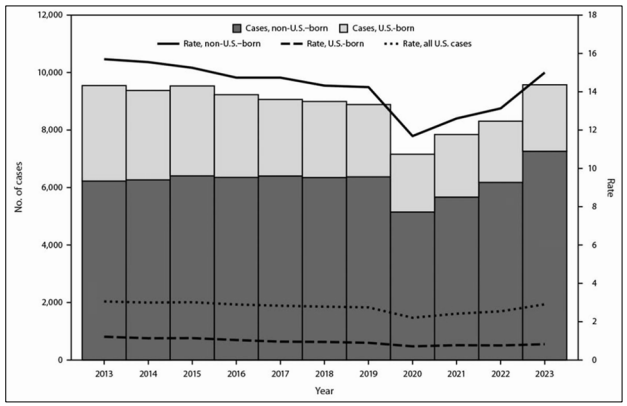
| Live vaccines | Severe immunosuppression |
|---|---|
| **Live vaccines** | |
| **Bacillus Calmette Guérin (BCG)** | Contraindicated |
| **Chikungunya (Ixchiq)** | Contraindicated |
| **Cholera (Vaxchora)** | No data, generally recommend against use |
| **Ebola (Ervebo)** | Consider |
| **Influenza, 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://www.cdc.gov/yellow-book/hcp/travelers-with-additional-considerations/immunocompromised-travelers.html revised for 2026

## 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/




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

## 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*


©2026 Infectious Disease Board Review, LLC

## T-SPOT.®*TB* and QuantiFERON®-TB Gold

- Enumerates effector T-cell response to stimulation with a combination of peptides simulating ESAT-6 and CFP10 (+ TB7.7 for QFN) antigens
- Detects prior exposure to:
  - *M. tuberculosis* complex organisms (*M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti)*
  - *M. kansasii, M. szulgai,* and *M. marinum*
- Not + with prior BCG vaccine (bacille Calmette–Guérin)
- Interpret test correctly:
  - If either test or PPD positive, take as positive
  - Borderline results = partway b/w + and negative
  - **Indeterminate results = assay did not work**

**Your patient has latent TB. Should and when should you start chemoprophylaxis? When can immunosuppressive medications be started?**

A. Start TB chemoprophylaxis ASAP as per guidelines. (Ensure no active TB, pulmonary or extrapulmonary.) Can start immunosuppression any time.

B. Avoid TB chemoprophylaxis. Too many side effects, and too much hassle.

C. Most of my patients had BCG vaccine as children, and test false + as older adults. I don't give TB chemoprophylaxis.

**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.

Excellent Prophylaxis is Paramount…
*and provides important clues for boards questions*

- Antivirals
- Pneumocystis/Toxoplasmosis
- Antifungals


©2026 Infectious Disease Board Review, LLC

# Cytomegalovirus Prevention

## Prophylaxis vs. Preemptive Therapy

**Antiviral Prophylaxis**
*Valganciclovir or Letermovir*

MORE COMMON

**Typically 3-6 months**

0 4 8 12 16 20 24

**Preemptive Monitoring**
*Once weekly for 12-16 weeks*

**Monitor weekly (PCR or pp65 Ag)** – *If CMV detected, treat until cleared*

0 4 8 12 16

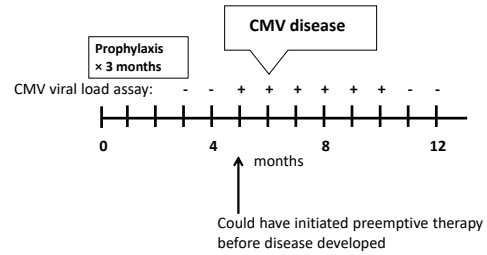
*Weeks Post-Transplant*

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

## Hybrid Strategy for SOT: CMV Surveillance After Prophylaxis

Consider "net state of immunosuppression"

- Weekly monitoring after end of prophylaxis, for ~12 weeks
- High risk (D+/R-) may be highest yield population (for late disease)
  - Other high-risk groups (potent immunosuppression)
- Guidelines experts use approach, not strongly evidence-based




Kotton CN et al,The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation, Transplantation 2025

**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)

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$277** letermovir 480 mg/day vs **US$4** valganciclovir 900 mg/day per goodrx.com (April 2026)

**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)

**OL6 Review of Basics: Transplant Infectious Disease**

*Speaker: Camille Kotton, MD, FAST, FIDSA*

©2026 Infectious Disease Board Review, LLC

**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<br>-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

## 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

## 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

## 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


©2026 Infectious Disease Board Review, LLC

## 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

## 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 | |

## 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

## 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
  - Breakthrough candidiasis
- Posaconazole
  - Usually covers mucormycosis (lower MICs than isavuconazole)


©2026 Infectious Disease Board Review, LLC

## Sources of Infection after Transplant

- Community-acquired
- Nosocomial
- Prior colonization
  - + Intraoperative *Aspergillus* culture w/ cystic fibrosis & lung transplant → OR 4.36 invasive aspergillosis (Luong *et al*, Transplantation 2014)
- Emerging
- Donor-derived infection
  - Organ graft, blood products

**Ten years of donor-derived disease: A report of the disease transmission advisory committee** *Am J Transplant.* 2021;21:689–702

Daniel R. Kaul[1] | Gabe Vece[2] | Emily Blumberg[3] | Ricardo M. La Hoz[4] | Michael G. Ison[5] | Michael Green[6] | Timothy Pruett[7] | Michael A. Nalesnik[8] | Susan M. Tlusty[2] | Amber R. Wilk[2] | Cameron R. Wolfe[9] | Marian G. Michaels[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!)**

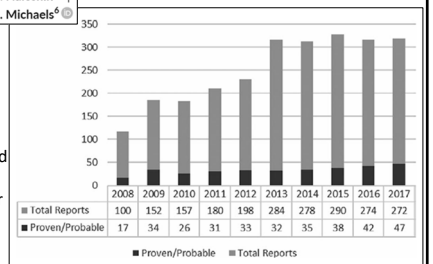



FIGURE 2 Total reports of potential donor transmission events by year

## 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)<br>Heart<br>Liver | N/A | Blood transfusion (received by donor) | 27 days prior to organ donation (received by donor) | 4 weeks<br>17 days<br>15 days | Dead (1)<br>Dead<br>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

## Syndromes


©2026 Infectious Disease Board Review, LLC

## 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

## 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

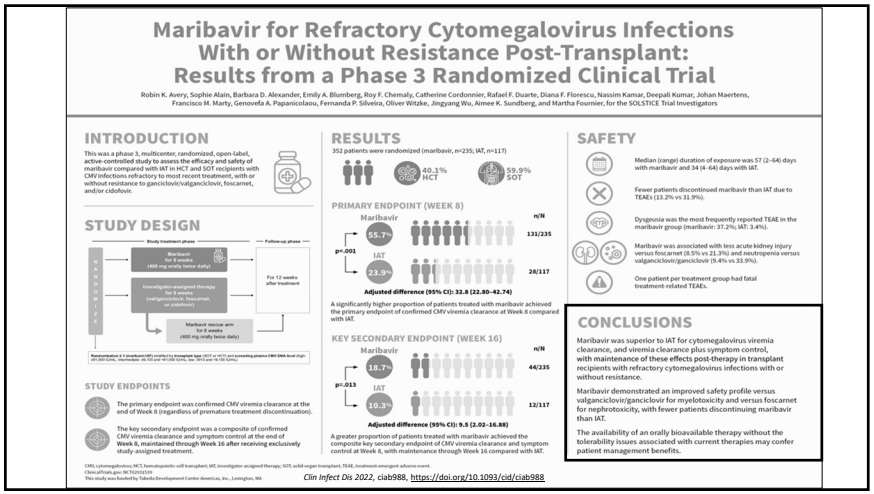
Check weekly CMV DNAemia (i.e. CMV viral load) on plasma (vs whole blood).
**Trend weekly until there are one-two negative/very low (<200 IU/ml) results, then stop therapy.**

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).

## 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*



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)

n/N

Maribavir 55.7% 131/235

p<.001

IAT 23.9% 28/117

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)

n/N

Maribavir 18.7% 44/235

p=.013

IAT 10.3% 12/117

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.

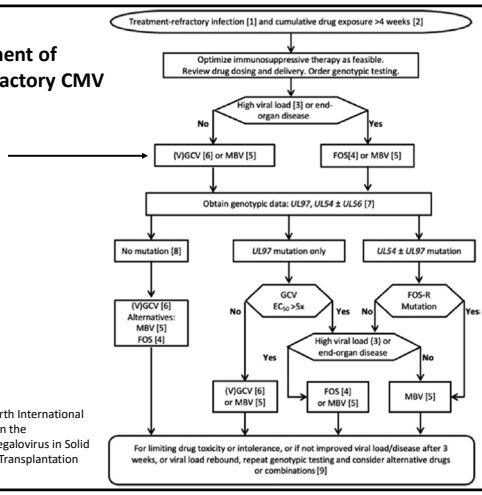
Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir for myelotoxicity and versus foscarnet for nephrotoxicity, with fewer patients discontinuing maribavir than IAT.

The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

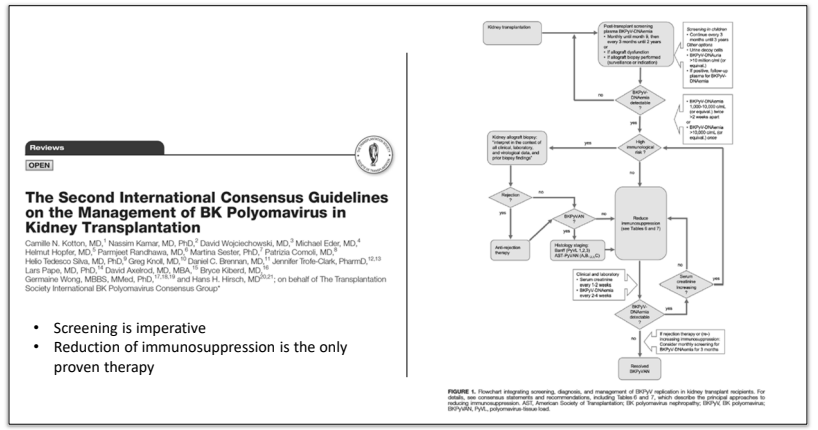
*Clin Infect Dis* 2022, ciab988, https://doi.org/10.1093/cid/ciab988


©2026 Infectious Disease Board Review, LLC

## 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



Reviews

OPEN

### The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

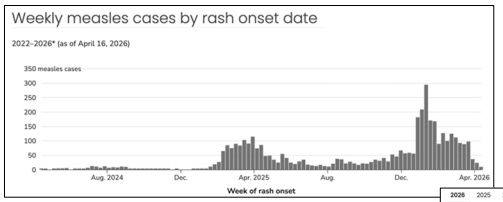
Camille N. Kotton, MD,[1] Nassim Kamar, MD, PhD,[2] David Wojciechowski, MD,[3] Michael Eder, MD,[4] Helmut Hopfer, MD,[5] Parmjeet Randhawa, MD,[6] Martina Sester, PhD,[7] Patrizia Comoli, MD,[8] Helio Tedesco Silva, MD, PhD,[9] Greg Knoll, MD,[10] Daniel C. Brennan, MD,[11] Jennifer Trofe-Clark, PharmD,[12,13] Lars Pape, MD, PhD,[14] David Axelrod, MD, MBA,[15] Bryce Kiberd, MD,[16] Germaine Wong, MBBS, MMed, PhD,[17,18,19] and Hans H. Hirsch, MD[20,21]; on behalf of The Transplantation Society International BK Polyomavirus Consensus Group*

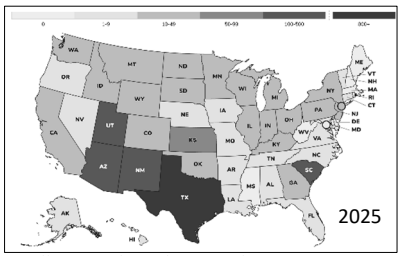
- Screening is imperative
- Reduction of immunosuppression is the only proven therapy

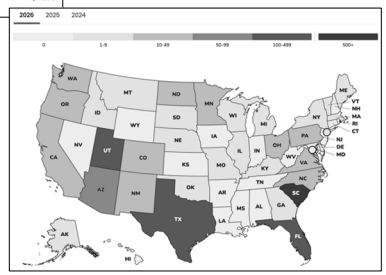


FIGURE 1. Flowchart integrating screening, diagnosis, and management of BKPyV replication in kidney transplant recipients. For details, see consensus statements and recommendations, including Tables 6 and 7, which describe the principal approaches to reducing immunosuppression. AST, American Society of Transplantation; BK polyomavirus nephropathy; BKPyV, BK polyomavirus; BKPyVAN, PyVL, polyomavirus-tissue load.

## Measles & USA




https://www.cdc.gov/measles/data-research/index.html 22 April 2026 accessed

## CDC: Post Measles Exposure Prophylaxis in Severely Immunocompromised Patients (2013)

- Unvaccinated/seronegative, within 6 days of exposure:
  - < 30 kg give gamma globulin IM 0.5 mL/kg max 15 mL
  - > 30 kg give IVIG 400mg/kg
- US, CDC (2013)[2]: "Immunocompromised patients. **Severely immunocompromised patients who are exposed to measles should receive IGIV prophylaxis regardless of immunologic or vaccination status** because they might not be protected by the vaccine."
- "Severely immunocompromised patients include **patients with severe primary immunodeficiency; patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in patients who have developed graft-versus-host disease; patients on treatment for ALL within and until at least 6 months after completion of immunosuppressive chemotherapy; and patients with a diagnosis of AIDS or HIV-infected persons with severe immuno-suppression."**

[2]McLean et al, Prevention of Measles, Rubella, Congenital Rubella Syndrome, and Mumps, 2013. Summary Recommendations of the Advisory Committee on Immunization Practices (ACIP), MMWR Recomm Rep . 2013 Jun 14;62(RR-04):1-34, https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm



©2026 Infectious Disease Board Review, LLC

Mass General Brigham

MGB Antimicrobial Stewardship Program

## Measles Post-Exposure Prophylaxis

This document provides current guidance for evaluation and management of asymptomatic individuals with exposure to measles and indications for measles post-exposure prophylaxis (PEP).

| | | |
|---|---|---|
| **Moderate to Severely Immunocompromised (any age)** | **Non-immune** (regardless of vaccine or measles IgG status) | < 12 months: IMIG 0.5 ml/kg (max dose = 15 mL) if no contraindications to IMIG[a]<br>≥ 12 months - IVIG 400 mg/kg if no contraindications to IVIG[a] |

https://partnershealthcare.sharepoint.com/:w:/r/sites/MGBAntimicrobialInfectiousDiseasesQualityCollaborativeASIDQC/_layouts/15/Doc.aspx?sourcedoc=%7B24AE2760-1707-477F-9D28-44A6C056001C%7D&file=MGB%20ASP%20-%20Measles%20PEP%20V.2.0.docx&action=default&mobileredirect=true

## Measles Post Exposure Prophylaxis: Challenges

- IVIG 400 mg/kg takes hours to infuse
- Strict respiratory infection control needed
  - Measles highly contagious
  - Might not want many immunocompromised in same infusion suite?
- Requires infusion suite or hospital level care
- Cost likely starts at several thousand dollars ($2500-10,000)
- Local IVIG supplies may not be robust enough in outbreak
- Duration of protection not known, concerning in ongoing outbreak
  - PKPD studies lacking

## The Dreaded Pulmonary Nodule

For the boards (and clinical medicine), consider the prophylaxis and what's not covered

Let the prophylaxis and epidemiology drive your differential diagnosis

## Who gets fungal infections?

- Post-solid organ transplant: Incidence of invasive fungal infections in the first year has been reported to be 3%[1]
  - Candidiasis (sterile space), esp liver transplant*surgery
  - Cryptococcal disease
    - Among most common causes of meningitis
  - Invasive aspergillosis in 1-15%[2]
    - Accounts for significant % of deaths in first year
    - Mortality dropping in recent times, however
  - Mucormycosis less common, higher mortality
- Stem cell transplant: similar, longer risk if graft-vs-host disease
- Non-transplant immunocompromised hosts: less frequent/"net state of immunosuppression"

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



©2026 Infectious Disease Board Review, LLC

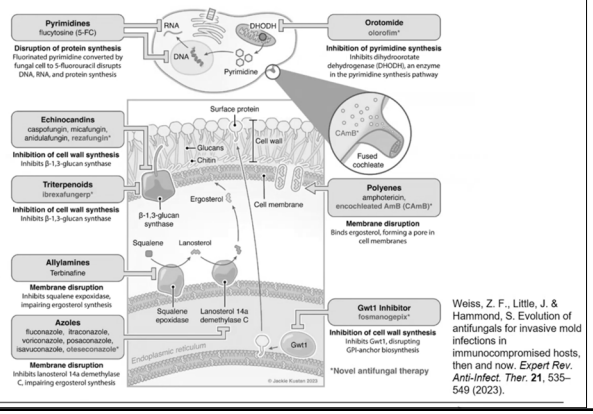
# Diagnostics

- 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)

# Diagnostics: Fungal Markers

| Diagnostic Assay | Specimen | Comments |
|---|---|---|
| Cryptococcal antigen | Blood, CSF | High sensitivity/specificity |
| 1,3 beta – D - glucan | Blood | Primarily for yeast;<br>Low sensitivity/moderate specificity<br>*Excellent for Pneumocystis* |
| Galactomannan | Blood, BAL, other body fluids | Primarily for Aspergillus;<br>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*<br>*Higher sensitivity with proven vs probable disease (60% vs 37% Sim BZ et al CID 2025)* |

# Antifungal Mechanisms of Action



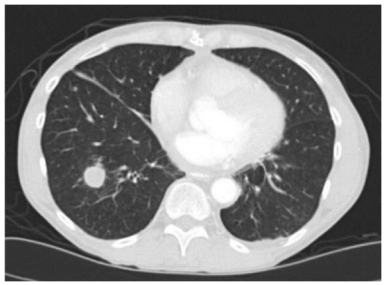

Weiss, Z. F., Little, J. & Hammond, S. Evolution of antifungals for invasive mold infections in immunocompromised hosts, then and now. *Expert Rev. Anti-Infect. Ther.* **21**, 535–549 (2023).

# Clinical Vignette

- 54 yo woman with history of primary systemic AL amyloidosis, complicated by cardiac amyloidosis, treated cytoxan/bortezomib/dexamethasone initially, followed by lenalidomide/dexamethasone
- Orthotopic cardiac transplant Feb 2016
- Autologous stem cell transplant, Day 0=7/11/16.
- CMV DNA VL on Day 0 was 29,800 IU/ml.
- Neutropenic sepsis with a blood culture on Day 5 with *Strep salivarius*.
- Ongoing fevers, new 2 cm pulmonary nodule by CT on Day 18


©2026 Infectious Disease Board Review, LLC





After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

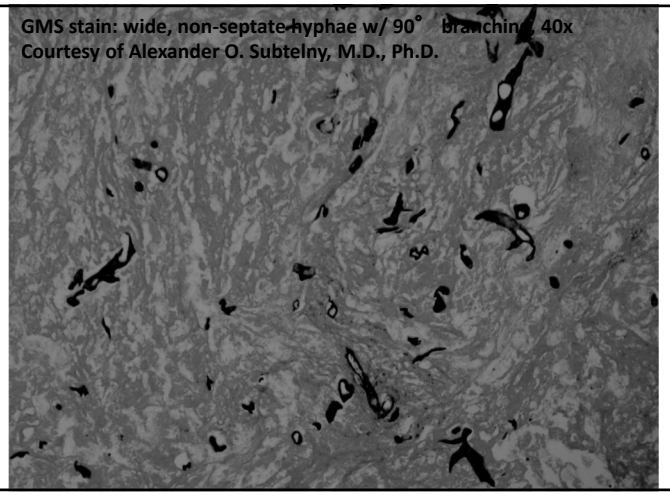
After ordering bronchoscopy, next best step?

- Start voriconazole
- Start posaconazole or isavuconazole
- Start amphotericin B product
- Start echinocandin (caspofungin/micafungin/anidulafungin)
- Combination therapy

- "She has had a dry cough but denies any sputum production, chest pain, SOB or headache. She has felt very well, and was quite determined to be discharged in the next few days."
- Voriconazole started
- She was underwent bronchoscopy, radial EBUS, washings, brushings and transbronchial biopsy → nonseptate hyphae seen
- Diagnosis: likely Zygomycetes
- She was switched from voriconazole to dual antifungal therapy with loading of isavuconazole and Ambisome.
- Repeat CT scan performed 2 days later showed significant increase in size of the nodule with new satellite lesions. She proceeded to RLL resection that evening by the cardiothoracic surgeons.


©2026 Infectious Disease Board Review, LLC






Very Rare RHIZOPUS SPECIES

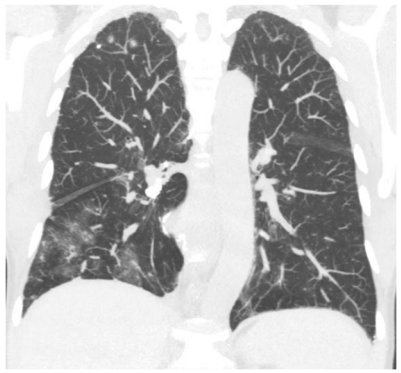
SUSCEPTIBILITY Performed at UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER, Dept of Pathology, San Antonio, TX

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).***

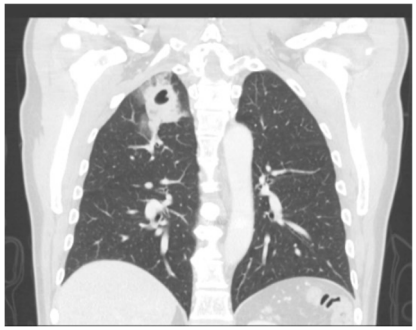


A year after transplant, she presented with disseminated zoster, new patchy infiltrates. Responded well to IV acyclovir.


©2026 Infectious Disease Board Review, LLC

## What's This?

- Man in 50s diagnosed with multiple myeloma in 2011 → autologous stem cell transplant in March 2019.
- Due to disease progression in June 2020, he was treated with daratumumab and pomalidomide. He received radiation therapy to the thoracic and cervical spine.
- He consented to participate in a clinical trial protocol and underwent CAR infusion in January 2021. On fluconazole and acyclovir prophylaxis.
- Routine screening PET 4 months later "new thick walled multiloculated cavitary lesion in the right upper lobe with surrounding groundglass and clustered nodularity is concerning for infection, including bacterial as well as atypical and fungal infections in an immunocompromised patient". No symptoms at all



## Epidemiology (ID fellow note)

- Living situation - lives with wife, 3 kids
- Outdoor exposures - rare, walks outside with dog in rode, has stopped dirt biking/hiking with thrombocytopenia
- Occupational exposures - Denies, works as a contractor for DoD, currently working at home
- Hobbies - mostly spending time at home right now
- Travel - Frequent travel pre-pandemic for work, has been to Australia, multiple countries in Asia and Europe, never to Africa or South America
- TB – no history of TB or known TB exposures; homeless or incarcerated? Denies
- Animals - Dog
- Food - raw or unpasteurized foods? Denies
- Dental work - None recent, does have a wisdom tooth pressing on a facial nerve
- Smoking - Denies
- Alcohol - Denies
- Recreational drugs - Denies
- Sex and prior STIs- Denies

## What would you do next?

A. Start voriconazole, loading dose then maintenance based on weight
B. Start "vancopime" (cefepime plus vancomycin)
C. Start azithromycin
D. A-C (all of the above)
E. Bronchoscopy

## Pseudomonas!

All other studies negative:

- BAL mycobacterial, fungal stains/cultures
- Cryptococcal antigen (blood)
- 1,3 beta D glucan (blood)
- Galactomannan (BAL and blood)
- Pathology: Bronchial epithelium with rare scattered neutrophils. Alveolated lung with fibroinflammatory changes and chronic inflammation. There is no evidence of malignancy. No microorganisms are seen on Brown-Hopps, GMS, Steiner, PAS-D, FITE, and AFB stains. Immunohistochemical stains for CMV, HSV, VZV, and adenovirus are negative. Trichrome and elastic stains were examined. The histologic findings are compatible with acute infection.

04/19/2021 1657 | 04/29/2021 1323 | Wound culture/smear [818905205] (Abnormal)
Other from Biopsy
RUL LUNG TBBX

Susceptibility

| | Pseudomonas aeruginosa MIC METHOD | |
|---|---|---|
| Amikacin | <=2 | Susceptible |
| Cefepime | 2 | Susceptible |
| Ceftazidime | 2 | Susceptible |
| Ciprofloxacin | <=0.25 | Susceptible |
| Levofloxacin | 1 | Susceptible |
| Meropenem | <=0.25 | Susceptible |
| Piperacillin-tazobactam | <=4 | Susceptible |
| Tobramycin | <=1 | Susceptible |

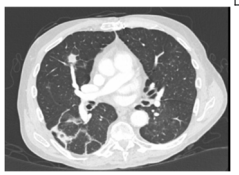

©2026 Infectious Disease Board Review, LLC

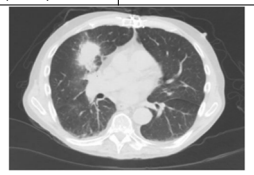
A **73-year-old heart transplant recipient admitted with fevers, weight loss, diarrhea, cough and a pulmonary mass**
Adam Stewart, MBBS, MPH and Carlos Portales, MD, Massachusetts General Hospital Transplant ID fellows

- 15 months PTA → DBD OHT (CMV D+R-, EBV D-/R+) for left ventricular non compaction cardiomyopathy
- 1 month PTA → cough, fevers, diarrhea.
- 25 days PTA CT chest → 1.6 cm nodule, attributed to pneumonia – Rx IV cefepime → Augmentin.
- Despite Rx, ongoing cough, malaise. Immunosuppression maintained
- Follow up CT scan done 9 days PTA → Stable 1.6 cm nodule
- Due to ongoing symptoms, presents for admission, admission CT → worsening 5.5 cm nodule!

| Workup | |
|---|---|
| Respiratory Viral Panel | Negative |
| Stool culture | Neg Salmonella, Shigella, Campylobacter (no PCR) |
| Serum GM | 0.05 |
| 1-3-BDG | Negative |
| EBV PCR | 1,270 (H) |
| CMV DNA | Negative |
| Respiratory culture | Yersinia enterocolitica |


*25 days PTA*


*9 days PTA*


*On day of admission*

**IV cefepime and amphotericin B were started. IS decreased. A lung biopsy was performed...**

**A 73-year-old heart transplant recipient admitted with fevers, weight loss, diarrhea, cough and a pulmonary mass**

- **Lung biopsy pathology:** Scattered EBV positive B cells in a background of organizing fibrosis, chronic inflammation, hemosiderin deposits and necrosis. Purulent necrosis seen. *Although the finding of EBV+ B cells raises the possibility of an EBV-associated PTLD , the tissue sample is scant and precludes definitive histologic subtyping. In addition, the unusual presence of purulent necrosis may reflect a concurrent bacterial infection, and an associated reactive process with increased EBV+ immunoblasts cannot be excluded*
- **No organisms seen on AFB, GMS or Steiner stains. CMV stain negative**
- **Lung biopsy culture: Moderate Yersinia enterocolitica**, no fungal or AFB growth.

| PTLD+ | PTLD- |
|---|---|
| Compatible syndrome | Low EBV PCR |
| Suggestive path | Recurrent growth of Yersinia in sputum |
| EBV D/R mismatch | Path suggestive of reactive EBV cells |

**EBV:1270**

IS decreased

Heme-Onc: Low likelihood PTLD - favor reactive EBV

**EBV 671**

14 days IV ceftriaxone → PO ciprofloxacin

Resolution of symptoms

Discharged

**EBV 36**

**EBV <35 x 3**


*2 weeks post- antibiotics*

**Diagnosis to date: Yersinia enterocolitica pneumonia in ICH**

Yersinia enterocolitica Pneumonia in a Heart Transplant Recipient
Transpl Infect Dis. 2025 Jan-Feb;27(1):e14422.

# Pneumonia

- 45yo s/p heart transplant 3 months earlier on posaconazole, atovaquone prophylaxis (not on TMP-SMX due to renal failure)
- New pneumonia, right middle lobe
- What is the cause?



Susceptibility

| | NOCARDIA NOVA COMPLEX MIC METHOD | |
|---|---|---|
| Comment | SEE NOTES | Note[1] |
| Amikacin | | Susceptible |
| Amoxicillin + Clavulanate | | Resistant |
| Ceftriaxone | | Susceptible |
| Ciprofloxacin | | Resistant |
| Clarithromycin | | Susceptible |
| Doxycycline | | Intermediate |
| Imipenem | | Susceptible |
| Linezolid | | Susceptible |
| Minocycline | | Susceptible |
| Moxifloxacin | | Resistant |
| Tobramycin | | Resistant |
| Trimethoprim/sulfamethoxazole | | Susceptible |

[1] SUSCEPTIBILITY TESTING Performed at the University of Texas Health Center at Tyler, Tyler TX



A 42-year-old woman underwent liver transplant.

-She was given three months of antiviral prophylaxis with valganciclovir, as both the donor and recipient were CMV IgG positive, and six months of trimethoprim-sulfamethoxazole.

-Two months later, she noticed this painful rash on her finger, as shown in the picture, with red streaking up her arm. What treatment would you initiate?

| Choices |
|---|
| **tecovirimat (Mpox)** |
| **linezolid** |
| **fluconazole** |
| **valacyclovir** |
| **voriconazole** |

This lesion was unroofed for sampling. Bacterial cultures grew *Staphylococcus epidermidis*. A serum cryptococcal antigen was negative. Fungal cultures were negative. Several days later, HSV-2 PCR of the lesion was positive, while HSV-1 and VZV were negative. **This is herpetic whitlow, which we usually associated with HSV-1 but can be from HSV-2.**


©2026 Infectious Disease Board Review, LLC

## Let's Switch to Parasites

## Toxoplasmosis

Epidemiology:

- 1988–1994 (NHANES III): ~22.5% of individuals in USA 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

## Clinical Vignette

64yo man from Dominican Republic with end-stage liver disease, chronic abdominal pain, listed for liver transplant

- Eosinophilia (up to 70%) x 6 months
- Recurrent enteric Gram negative bacteremias
- Fluffy pulmonary infiltrates
- What does he have?

## 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

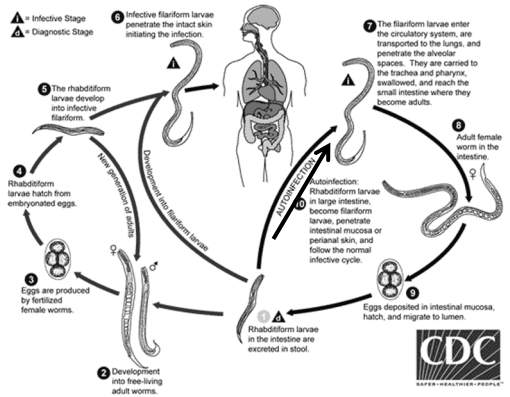

©2026 Infectious Disease Board Review, LLC

# Strongyloides

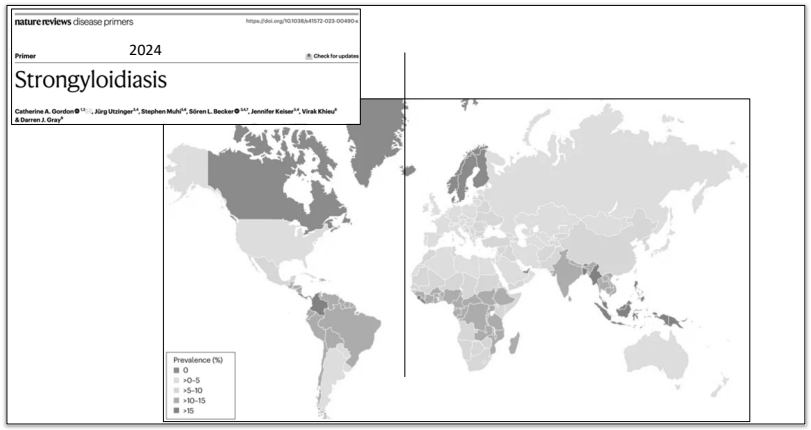
- Nematode “roundworm”
- 100-200 million people worldwide are infected
- Autoinfection*
- >50% mortality immunocompromised patients with disseminated disease



## *Strongyloides stercoralis* lifecycle




http://www.cdc.gov/dpdx/strongyloidiasis/




On-call fellow in the night: “the OSH says there are parasites in the sputum”

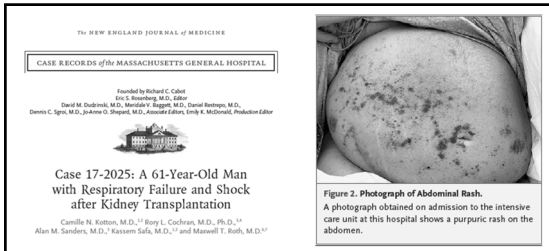
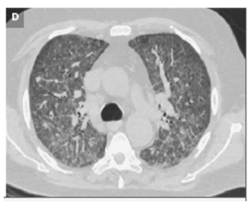
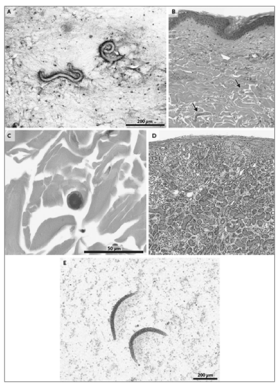





Figure 2. Photograph of Abdominal Rash.
A photograph obtained on admission to the intensive care unit at this hospital shows a purpuric rash on the abdomen.





DR. CAMILLE N. KOTTON’S DIAGNOSIS

Donor-derived disseminated strongyloidiasis.

**OL6 Review of Basics: Transplant Infectious Disease**

*Speaker: Camille Kotton, MD, FAST, FIDSA*

©2026 Infectious Disease Board Review, LLC

## 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 [93]

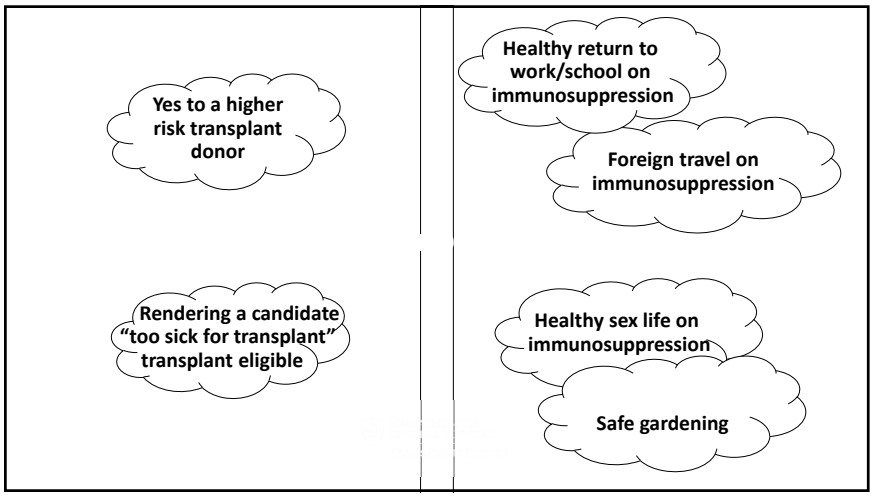
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

**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)."

## 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





©2026 Infectious Disease Board Review, LLC




## Cardinal Rules 2026: 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




**OL6 Review of Basics: Transplant Infectious Disease**

*Speaker: Camille Kotton, MD, FAST, FIDSA*

©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

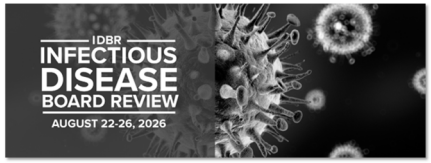
# OL7

# Even More Worms

**Edward Mitre, MD**

**©2026 Infectious Disease Board Review, LLC**

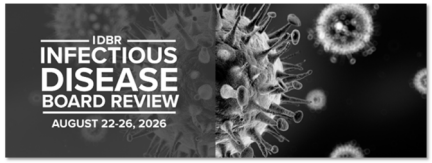
COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# 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.




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Major Helminth Pathogens

TREMATODES

Blood flukes
- *Schistosoma mansoni*
- *Schistosoma japonicum*
- *Schistosoma haematobium*

Liver flukes
- *Fasciola hepatica*
- *Clonorchis sinensis*
- *Opisthorchis viverrini*

Lung flukes
- *Paragonimus westermani*

Intestinal flukes
- *Fasciolopsis buski*
- *Metagonimus yokagawai*

CESTODES

Intestinal tapeworms
- *Taenia solium*
- *Taenia saginata*
- *Dibothriocephalus latus*
- *Hymenolepis nana*

Larval cysts
- *Taenia solium*
- *Echinococcus granulosus*
- *Echinococcus multilocularis*

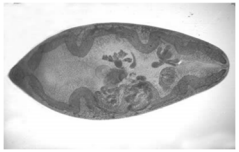
NEMATODES

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)*

## Trematodes (Flukes)

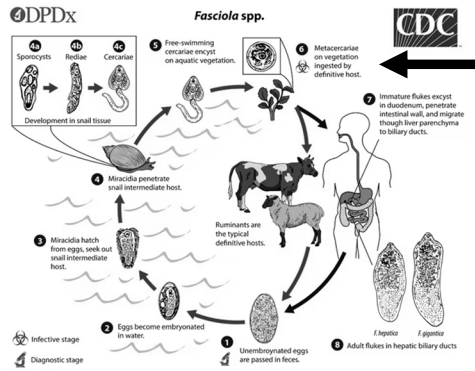
- Flat, fleshy, leaf-shaped worms
- Usually have two muscular suckers
- Usually hermaphroditic (except Schistosomes)
- Require intermediate hosts (usually snails or clams)
- Praziquantel treats all (except *Fasciola hepatica*)



*Paragonimus* (CDC DpDx)


©2026 Infectious Disease Board Review, LLC

## *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

## *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

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)




*F. hepatica*
(CDC DpDx)

## *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**

## *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:

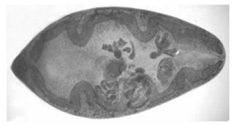
- *Fever, cough, diarrhea during acute migration*
- *Later, may have chest pain as worms migrate through lungs*
- *Can develop chronic pulmonary symptoms*

Dx: Sputum and/or stool exam for eggs, serology

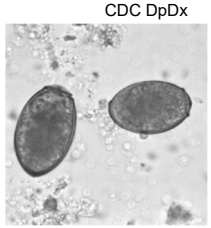
*NOTE: Cases of Paragonimus kellicotti acquired in U.S. by ingestion of raw crayfish in rivers in Missouri!*

CID 2009 Sep 15;49(6):e55-61.

Clin Microbiol Rev 2013 Jul;26(3):493-504



CDC DpDx



CDC DpDx


©2026 Infectious Disease Board Review, LLC

# 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

# 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*

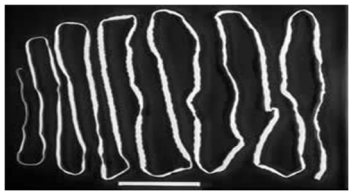
NEMATODES

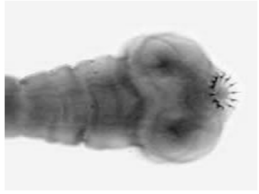
Intestinal
- *Ascaris lumbricoides*
- *Ancylostoma duodenale*
- *Necator americanus*
- *Trichuris trichiura*
- *Strongyloides stercoralis*
- *Paracapillaria philippinensis*
- *Enterobius vermicularis*

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)*

# Cestodes (Tapeworms)

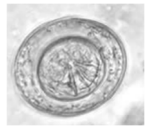
- All (except *D. latum)* have suckers with surrounding hooklets on the scolex (head) to attach to intestinal lining
- Have flat, ribbon-like bodies composed of proglottid segments which contain reproductive organs
- Have no digestive systems (food absorbed through soft body wall of worm)



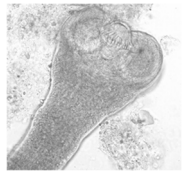


# *Hymenolepis nana*

"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

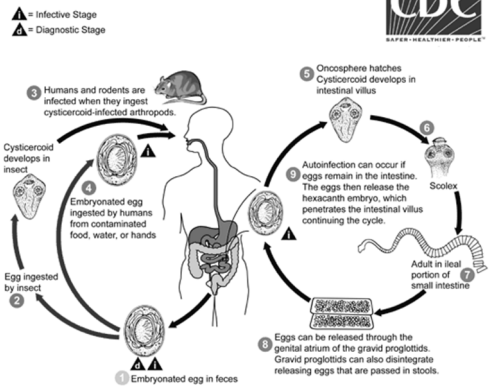


*H. nana* scolex in stool sample
(note the hooklets and suckers)
CDC DpDx


©2026 Infectious Disease Board Review, LLC

## *Hymenolepis nana*






## *Echinococcus multilocularis*

Fox/rodent lifecycle

Causes an infiltrative, tumor-like growth in liver

- → poorly demarcated
- → has a semi-solid nature (does not form large cysts)

*E. granulosus* *E. multilocularis*



*Lancet 2003,362:1295-304*

## 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)*

## Nematodes (Roundworms)

- Non-segmented round worms
- Flexible outer coating (cuticle)
- Muscular layer under the cuticle
- Nervous, digestive, secretory, and reproductive systems

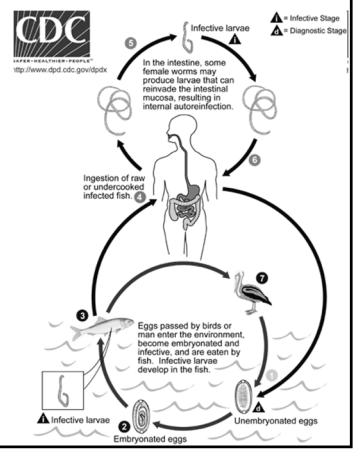



©2026 Infectious Disease Board Review, LLC

## 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

## *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

## *Paracapillaria philippinensis*

Pathogenesis:

Eat infected raw fish

→ larvae released into intestine

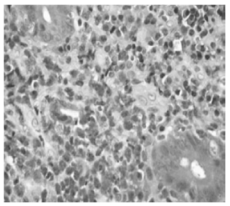
→ grow to adults which burrow in mucosa

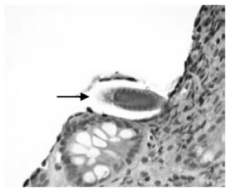
→ female worms lay eggs (oviparous)

→ some female worms are larviparous

→ some larvae burrow into the intestinal lining and develop into adults

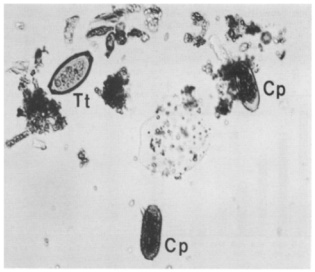
→ over weeks to months the worm burden increases (from a few worms to tens of thousands) and symptoms progress





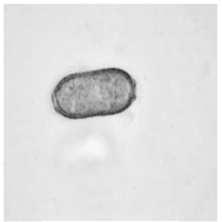
N Engl J Med 2008;359:75-80.

## *Paracapillaria philippinensis*




1. Eggs of *C. philippinensis* (Cp) compared with an egg of *T. trichiura* (Tt). Magnification, ×160.

*Cross J, Clin Micr Reviews, 1992*



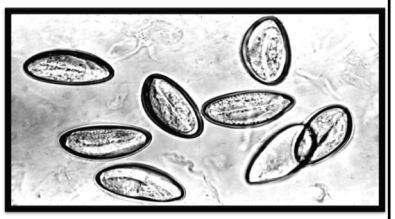
N Engl J Med 2008;359:75-80.

Dx: stool o/p (eggs similar to Trichuris)

Rx: 10 d course albendazole + supportive Rx (IVF, replete electrolytes, etc.)


©2026 Infectious Disease Board Review, LLC

## *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

## 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.

## 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.

## 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



©2026 Infectious Disease Board Review, LLC

# 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*

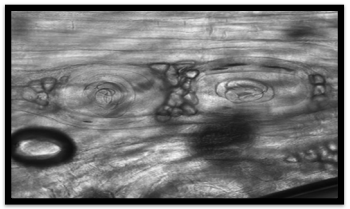
Tissue Invasive
- *Wuchereria bancrofti*
- *Brugia malayi*
- *Onchocerca volvulus*
- *Loa loa*
- *Trichinella spiralis*
- *Angiostrongylus cantonensis*
- *Anisakis simplex*
- *Toxocara canis/cati*
- *Baylisascaris procyonis*
- *Gnathostoma spinigerum*
- *(Dracunculus medinensis)*

# *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

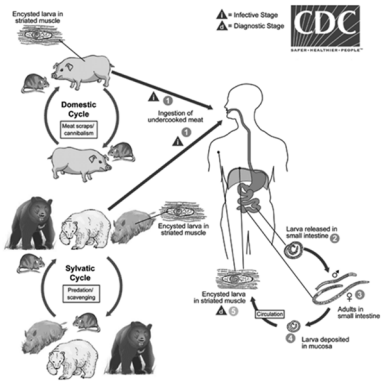


CDC DPDx

**Diagnosis:**
- Serologies are supportive
- + Biopsy is definitive

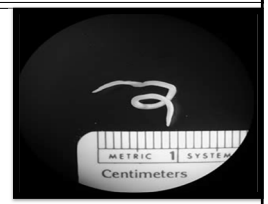
**Treatment:**
- Albendazole + steroids

# *Trichinellosis*




# 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


©2026 Infectious Disease Board Review, LLC

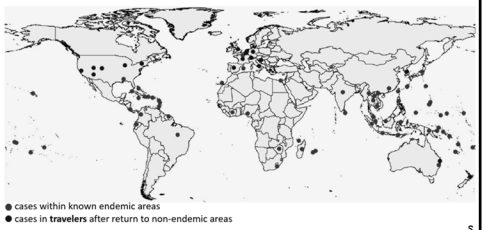
# Angiostrongylus

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*




*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

# 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

# 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)

# 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*
E. *Anyclostoma braziliense*


©2026 Infectious Disease Board Review, LLC

## 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***
E. *Anyclostoma braziliense*

## Toxocariasis (and Baylisascariasis)

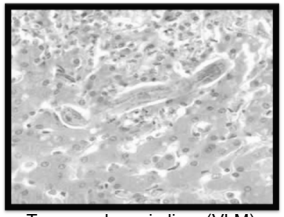
Due to dog (*Toxocara canis*), cat (*Toxocara cati*), and raccoon (*Baylisascaris procyonis*) ascarids.

Humans acquire infection by ingestion of animal feces.
In humans → larvae hatch in intestine and migrate to liver, spleen, lungs, brain, and/or eye.

**Symptoms**

Visceral Larva Migrans (VLM)
usually 2-5 year olds
fever, eosinophilia, hepatomegaly
also wheezing, pneumonia, splenomegaly

Ocular Larva Migrans (OLM)
often in 10-15 year olds
retinal lesions that appear as solid tumors


Toxocara larva in liver (VLM)

***Baylisascaris* often more severe and more likely to cause CNS disease (eosinophilic meningitis)**

CDC DPDx

## Toxocariasis

Dx: clinical picture + Toxocara antibody testing
(serum and intraocular fluid by ELISA testing)

NOTE: Toxocara IgG is only supportive b/c many individuals have + Ab due to prior exposure

Rx: usually self-limited disease
acute VLM or OLM can be Rx with albendazole and steroids

## Gnathostoma spinigerum and hispidum

**Undercooked freshwater fish (ceviche!), frogs, birds, reptiles**
Asia (esp. Thailand), Central/South America, parts of Africa

→ Disease due to migrating immature worms
→ Often with peripheral eosinophilia
→ 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


©2026 Infectious Disease Board Review, LLC

## What is this?



Emerging Guinea Worm.

## 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

**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

# Good Luck!

Ed Mitre
edwardmitre@gmail.com



©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL8

# Bone and Joint Infections

**Sandra Nelson, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Bone and Joint Infections

**Sandra B. Nelson MD**

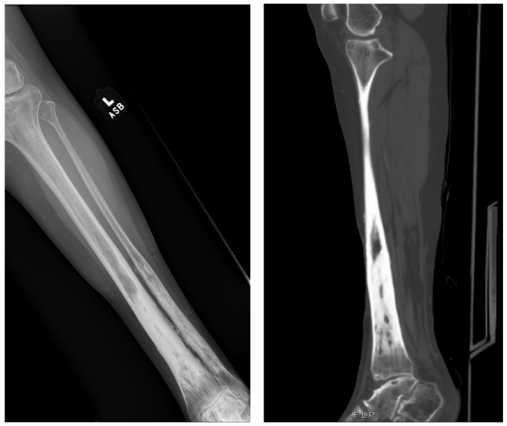
**Massachusetts General Hospital**
**Harvard Medical School**

8/11/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Osteomyelitis







## Question #1

- 57-year-old male presented with 3 months of progressive lower back pain.
- He denied fevers or chills, but reported 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







©2026 Infectious Disease Board Review, LLC

## 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



## 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



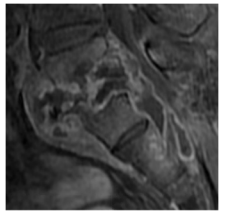
## Vertebral osteomyelitis: diagnosis



- Imaging pearls
  - MRI the most sensitive test 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



## 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





©2026 Infectious Disease Board Review, LLC

## 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



## Hematogenous osteomyelitis: testable points

- Imaging studies:
  - MRI is the most sensitive imaging study for diagnosis
  - Plain films and CT are useful in subacute and chronic infection
  - Bone scan is an excellent "rule-out" test; should not be used to confirm infection
  - Imaging studies not useful as a test of cure
- Diagnosis can only be confirmed through bone histopathology and culture
  - Treatment for osteomyelitis in the absence of proven diagnosis may be acceptable
  - Limited role for molecular diagnostics
- Optimal therapy remains an evolving target
  - 6 weeks of antimicrobial therapy commonly used
  - Oral therapy supported in many circumstances



## Diabetic foot osteomyelitis: testable points



- Probe to bone test is sufficiently specific to confirm diabetic foot osteomyelitis
  - but not other forms of osteomyelitis
- Superficial culture should not be used to inform microbial etiology
- No need to empirically target Pseudomonas unless:
  - Moderate to severe presentation with macerated ulcer and/or tropical humid climate
- Antibiotic duration (IWGDF guidelines)
  - 2-5 days if infected bone fully resected
  - 1-2 weeks if residual soft tissue infection after resection
  - 3 weeks if residual osteomyelitis following bone resection
  - 6 weeks if no surgical debridement or nonviable bone

IWGDF: International Working Group on the Diabetic Foot



## Septic Arthritis







©2026 Infectious Disease Board Review, LLC

## 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.

Laboratory Studies
WBC 13,000 (72% pmns)
ESR 62 CRP 47.7 mg/L
ANA 1:40, speckled pattern

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.

Synovial Fluid Sampling (right ankle):
34,500 WBCs/μL (83% neutrophils)
Negative gram stain
No crystals

Plain films showed bilateral tibiotalar effusions



## 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



## 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



## Septic arthritis: clinical pearls

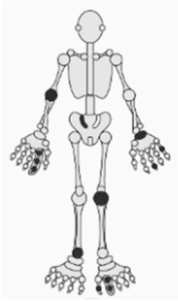
- Synovial fluid cell counts: no diagnostic threshold
  - Higher probability of septic arthritis if WBC >50,000/$mm^3$
  - Lower cell counts do not exclude septic arthritis
- More subtle presentations in immunocompromised hosts and with indolent organisms
  - Subacute history
  - Lower synovial fluid cell counts
- Negative cultures and/or delayed culture positivity:
  - think Gonococcus, HACEK, Lyme, Mycoplasma





©2026 Infectious Disease Board Review, LLC

## 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

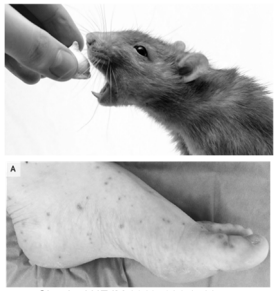
Other causes of polyarthritis
- Rat bite fever
- Disseminated gonococcus
- Viral infection
- Non-infectious

PWID: Persons who inject drugs



## Rat bite fever

- Seen in children, pet store employees, laboratory technicians
- Polyarthritis (usually symmetric, often migratory)
- Associated with fever, maculopapular and/or pustular rash
- *Streptobacillus moniliformis*
  - in Asia *Spirillum minus*
- Rx: penicillin

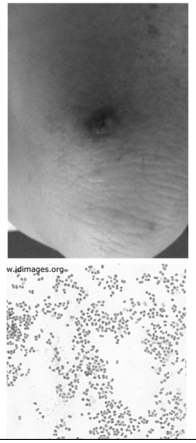


Giorgiutti NEJM 2019: 381:1762



## Gonococcal arthritis

- Tenosynovitis, arthralgias, skin lesions
  - Especially extensor surface tenosynovitis
  - Migratory arthralgias
- Purulent arthritis
  - May be polyarticular; knees most common
  - Lower synovial fluid cell counts more common
- Asymptomatic mucosal phase predisposes
  - Dissemination more common in women
- Dx: mucosal site (cervical, urethral) is highest yield
  - Blood (<30%) and synovial fluid (<50%) cultures lower yield
  - Compatible clinical syndrome





## Viral arthritides

- Symmetric polyarthritis, often involving small joints
- Often associated with fever and rash
- Diagnose serologically (+IgM or 4-fold rise in IgG titer) or by viral pcr

| Viral causes of polyarthritis | Clinical and Epidemiologic Clues |
|---|---|
| Parvovirus B19 | History of exposure to children (often a teacher or parent); more common in women. Hands most common; can be severe. |
| Rubella | Non-immune (non-US born).<br>Cervical lymphadenopathy, fever, rash. |
| Hepatitis B Virus | Serum-sickness like reaction, resolves with development of jaundice; associated with polyarteritis nodosa (PAN) |
| Hepatitis C Virus | Immune complex arthritis associated with cryoglobulinemia |
| Alphaviruses (esp. Chikungunya) | Travel to or residence in endemic areas |

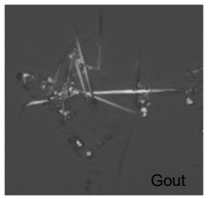


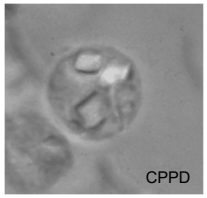


©2026 Infectious Disease Board Review, LLC

## 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
  - CPPD and septic arthritis can coexist
  - CPPD rarely has cell count >30,000
  - CPPD rarely associated with high fever
  - Rhomboid-shaped calcium pyrophosphate dihydrate crystals


Gout


CPPD

21

## 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 ….





Coelho BMJ Case Reports 2017-222475

22

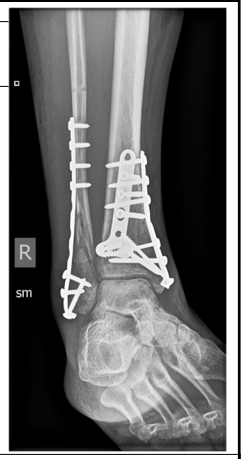
## Implant Infections



22

## Question #3

- 44-year-old healthy woman suffered a closed right ankle pilon fracture and underwent open reduction internal fixation (ORIF)
- Chronically discharging wound despite courses of cephalexin and trimethoprim-sulfamethoxazole
- Two months after ORIF, deep wound culture grows *Staph aureus*
  - Sensitive to ciprofloxacin, clindamycin, levofloxacin, erythromycin, gentamicin, methicillin, rifampin, tetracycline, trimethoprim-sulfamethoxazole, vancomycin
- Plain films: hardware intact; fracture not yet consolidated
- She is hospitalized and started on IV cefazolin




24



©2026 Infectious Disease Board Review, LLC

## Question #3

**What do you recommend next?**

A. No surgical debridement; cefazolin for 6 weeks
B. Surgical debridement with hardware removal; 6 weeks of trimethoprim-sulfamethoxazole
C. Surgical debridement with hardware removal; 6 weeks of trimethoprim-sulfamethoxazole and rifampin
D. Surgical debridement without hardware removal; 6 weeks of levofloxacin and rifampin
E. Surgical debridement with hardware exchange; 6 weeks of levofloxacin and rifampin

25

## Question #3

**What do you recommend next?**

A. No surgical debridement; cefazolin for 6 weeks
B. Surgical debridement with hardware removal; 6 weeks of trimethoprim-sulfamethoxazole
C. Surgical debridement with hardware removal; 6 weeks of trimethoprim-sulfamethoxazole and rifampin
**D. Surgical debridement without hardware removal; 6 weeks of levofloxacin and rifampin**
E. Surgical debridement with hardware exchange; 6 weeks of levofloxacin and rifampin

26

## Fracture-related infections

Goals include both fracture consolidation and infection eradication
Removal of hardware depends upon fracture healing and timeline
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<br>Revision fixation | Hardware removal |
| **Antimicrobial Management** | Pathogen-directed therapy<br>Addition of rifampin if Staph<br>Duration often 12 weeks or until fracture heals | Pathogen-directed therapy<br>Duration often six weeks | Pathogen-directed therapy<br>Duration often two weeks following hardware removal |

27

## Antimicrobial treatment of bone and joint infection

- Few drugs are FDA approved for bone and joint infection
- Comparative studies are limited
- Duration of therapy an evolving target
- Suppression is commonly employed with infection in setting of retained hardware, but highly variable
  - decision to suppress (and how long to suppress) unlikely to be on boards

28


©2026 Infectious Disease Board Review, LLC

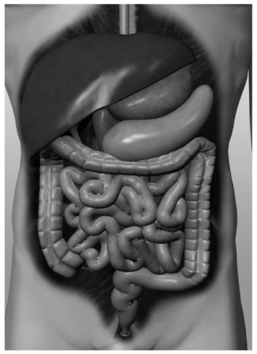
## Oral antibiotics for bone and joint infections

- Now supported by a large body of literature for definitive therapy of bone and joint infection
- 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 / bacteremia)
  - Malabsorption
  - Not well studied for drug-resistant bacteria (e.g. MRSA)



29

## Highly bioavailable oral therapy



| |
|---|
| Amoxicillin / amoxicillin-clavulanate |
| Cefadroxil / cephalexin |
| Ciprofloxacin / levofloxacin / moxifloxacin |
| Clindamycin |
| Doxycycline / minocycline |
| Linezolid / tedizolid |
| Metronidazole |
| Rifampin |
| Trimethoprim-sulfamethoxazole |

* No preferred regimen; most data to support quinolone + rifampin in Staphylococcal PJI

30

## 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)
  - Not as well established for other bacterial pathogens
- Specifics
  - Never to be used in monotherapy of established infection
  - Evidence supports quinolones as the best partner drug, but acceptable alternatives
  - Should not be used prior to surgical debridement and until partner drug therapeutic
  - Multiple drug interactions (primarily via Cyp 3A4 pathway)

31

## Periprosthetic Joint Infection (PJI)



32

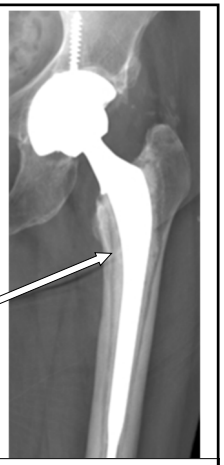


©2026 Infectious Disease Board Review, LLC

## PJI: diagnostic pearls

- Diagnosis of early and late hematogenous PJI 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<br>% pmns > 90 | WBC > 3000/μL<br>% pmns > 75 |
| **Synovial fluid Alpha-defensin** | Usually positive | Usually positive |



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

33

## PJI: management



| Surgical Procedure | Indication | Antimicrobial Therapy* |
|---|---|---|
| Debridement and implant retention (exchange of modular components) | Early surgical site infection<br>Acute hematogenous<br>Well-fixed components | 12 weeks antibiotics (IV/PO)<br>Rifampin if Staph |
| 1-stage exchange | Acute and subacute infections<br>Healthy soft tissues<br>Sensitive organisms | 12 weeks antibiotics (IV/PO)<br>Rifampin if Staph |
| "2-stage" exchange<br>Antibiotic spacer<br>(With or without 2nd stage) | Chronic infections<br>Sinus tracts<br>Resistant organisms | 6 weeks antibiotics (IV/PO) |

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

*2013 IDSA Guidelines; modified based on DATIPO study

34

## 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)

35

## 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

36



©2026 Infectious Disease Board Review, LLC

## 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

37

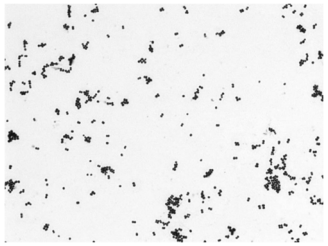
## Antimicrobial cement (PMMA)

- "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
  - Acute kidney injury seen in important minority
  - Allergy reported but rare



38

## Microbiology of Musculoskeletal Infections



39

## 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.

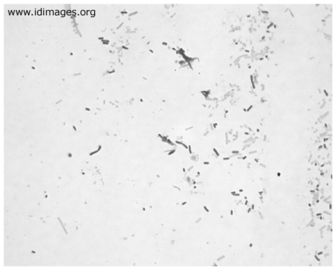
40



©2026 Infectious Disease Board Review, LLC

## Question #5

Culture growth at 3 days incubation



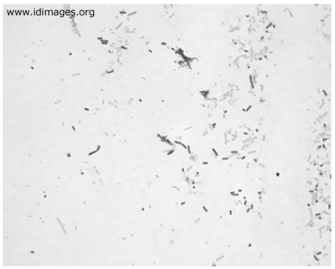

**What is the most likely organism?**

A. *Serratia marcescens*
B. *Salmonella heidelberg*
C. *Staphylococcus aureus*
D. *Kingella kingae*
E. *Pasteurella multocida*



## Question #5

Culture growth at 3 days incubation



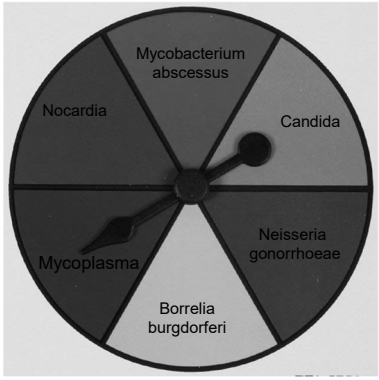

**What is the most likely organism?**

A. *Serratia marcescens*
**B. *Salmonella heidelberg***
C. *Staphylococcus aureus*
D. *Kingella kingae*
E. *Pasteurella multocida*



## Guess the Bug

Musculoskeletal Edition




## 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







©2026 Infectious Disease Board Review, LLC

## 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

45

## 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

46

## 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

47

## Pasteurella species



- Clinical
  - Direct inoculation (bite)
  - Hematogenous spread
  - Rapid clinical onset
- Epidemiology
  - Exposure to cats/dogs
  - Bite history not always elicited in hematogenous infection

48



©2026 Infectious Disease Board Review, LLC

## *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



49

## *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



50

## 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

51

## 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



Karrakchou BMC Dermatology 2020

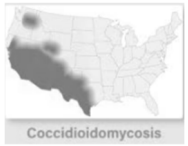
52



©2026 Infectious Disease Board Review, LLC

## Endemic mycoses

- Coccidioides 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










53




**Thank you!**

54



©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL9

# Penicillin Allergy

**Sandra Nelson, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Penicillin Allergy

**Sandra B. Nelson, MD**

**Massachusetts General Hospital**
**Harvard Medical School**

8/11/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Penicillin (PCN) Allergy: Premise

- 10% of the US population have penicillin allergy label
- Majority with history of PCN allergy can safely receive penicillins (with appropriate evaluation and testing)
  - Some reactions are not allergic
  - Allergies often wane with time
  - Allergic reactions do not always recur
- 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






## Approach to Penicillin Allergy

- Penicillin allergy history
  - Type of reaction
  - Timeline of reaction
  - Severity of reaction
- Assess need (and timeline) for beta-lactam drug



**OL9 Penicillin Allergy**
*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## Question #1

A 44-year-old previously healthy woman was diagnosed with septic arthritis of the knee due to *Streptococcus dysgalactiae*. After surgical debridement and several days of IV ceftriaxone, she was discharged on high-dose oral amoxicillin. Two weeks following discharge she developed fever and malaise, followed by a generalized maculopapular rash involving her torso and extremities.

On examination, the rash had become confluent in areas and involved >50% of her skin. There was no mucosal involvement. Other notable examination findings included facial edema and generalized lymphadenopathy. The surgical incision was healing well without effusion or erythema.

Laboratory studies:
WBC 12.6 (68% pmns;13.5% eosinophils) Hgb 11.4 PLT 488
BUN 24 Creat 1.7
AST 78 ALT 112 Alk Phos 144 Tbili 0.8



## Question #1

**What do you advise?**

A. Continue amoxicillin with close monitoring
B. Stop amoxicillin, start cefadroxil
C. Admit to the hospital, stop amoxicillin, resume IV ceftriaxone
D. Admit to the hospital, stop amoxicillin, start vancomycin
E. Admit to the hospital, stop amoxicillin, start vancomycin and corticosteroids



## Question #1

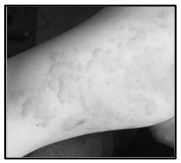
**What do you advise?**

A. Continue amoxicillin with close monitoring
B. Stop amoxicillin, start cefadroxil
C. Admit to the hospital, stop amoxicillin, resume IV ceftriaxone
D. Admit to the hospital, stop amoxicillin, start vancomycin
**E. Admit to the hospital, stop amoxicillin, start vancomycin and corticosteroids**

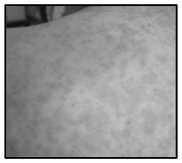


## Deciphering Cutaneous Reactions

- IgE-mediated reactions (urticaria)
  - Occur within minutes to hours, resolve within 24 hours
  - Often recurs with repeat exposure
  - Wheal and flare appearance
  - Isolated urticaria may be considered non-severe



- Benign T-cell mediated
  - Morbilliform or maculopapular, usually pruritic
  - May have associated eosinophilia
  - Usual onset days to weeks
  - Persists longer than 24 hours; resolves over days to weeks
  - May not recur with subsequent exposure
  - Can "treat through" with monitoring if drug essential



Shenoy JAMA 2019;321:188



**OL9 Penicillin Allergy**
*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## Severe Cutaneous Adverse Reactions (SCARs)

- T-cell mediated
- Types
  - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - Acute Generalized Exanthematous Pustulosis (AGEP)
  - Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS/TEN)
- Common Features:
  - Delayed onset
  - Blistering
  - Mucosal involvement
  - Severe skin desquamation
  - Organ involvement

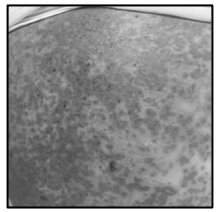




Shenoy JAMA 2019;321:188 9

## DRESS Syndrome

- Onset 10-14 days after drug exposure but may be longer
- Clinical Features:
  - Rash (often morbilliform, but may be pleomorphic)
  - Facial edema
  - Generalized lymphadenopathy
  - Organ involvement (renal and hepatic most common)
  - Eosinophilia and atypical lymphocytosis
- Most common implicated antimicrobials:
  - Vancomycin, trimethoprim-sulfamethoxazole
  - Also β-lactams, anti-TB medications, dapsone, minocycline
- Treatment: drug discontinuation, prolonged steroids



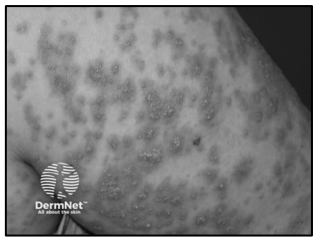


DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms

Kroshinsky et al. NEJM 2024; 391:2242 10

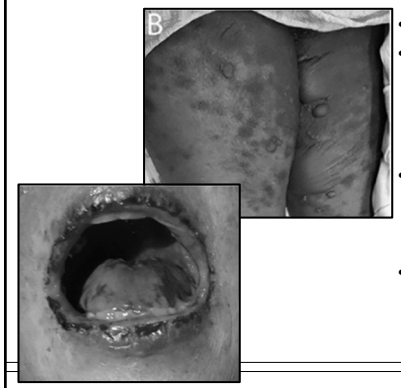
## AGEP

- Onset earlier, within 24-72 hours
- Clinical features:
  - Fever and rash (with small pustules)
  - Desquamation and mucosal involvement less common than DRESS
- Implicated antimicrobials
  - β-lactams, macrolides, clindamycin, fluoroquinolones
- Treatment
  - Drug discontinuation, topical steroids
- Less severe than DRESS




AGEP: Acute Generalized Exanthematous Pustulosis 11

## Stevens-Johnson Syndrome




- Onset 5-28 days after drug exposure
- Clinical features:
  - Fever, URI symptoms, cough
  - Then erythematous, targetoid, annular, or purpuric macules that progress to flaccid bullae
  - Mucosal involvement common (oral, ocular, genital)
- Implicated antimicrobials:
  - Trimethoprim-sulfamethoxazole most common
  - Also: β-lactams, fluoroquinolones, macrolides, nitrofurantoin
- Treatment:
  - Drug discontinuation, wound care
  - Steroids and other immunomodulators

Shah et al. Am J Clin Dermatol 2024;25:891 12

**OL9 Penicillin Allergy**

*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## Question #2

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 three years ago. She is delirious and not able to corroborate the history; no additional documentation of the reaction is available.



## Question #2

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



## Question #2

You are asked about optimal antibiotic treatment

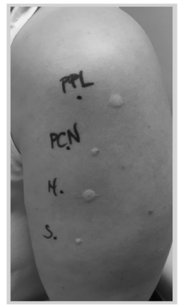
**What do you advise?**

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



## 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



**OL9 Penicillin Allergy**
*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

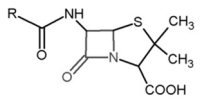
## Options for Approaching PCN Allergy

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

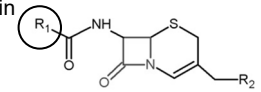
17

## PCN Allergy and Use of Cephalosporins

- Significant cross reactivity rare
  - Based on R1 side chain structure
- For IgE mediated PCN allergy:
  - Use structurally dissimilar cephalosporin without prior testing
  - Use structurally similar cephalosporin after PCN skin testing and amoxicillin challenge
- Mild delayed drug rash:
  - Any cephalosporin OK
- Avoid if severe reaction (e.g. SCAR) to PCN



Penicillins



Cephalosporins

18

## Putting it all together: penicillin reactions (IgE)

| | |
|---|---|
| Isolated urticaria | If PCN or cross-reactive cephalosporin indicated: PCN Skin testing<br>If positive: desensitization or alternative therapy<br>If negative: test dose amoxicillin or desired drug<br><br>Safe to administer non-cross-reactive cephalosporin |
| Extensive urticaria<br>Urticaria with anaphylaxis or angioedema | PCN Skin testing<br>If positive: desensitization or alternative therapy<br>If negative: test dose amoxicillin or desired drug |

19

## Putting it all together: non-IgE penicillin reactions

| | |
|---|---|
| Benign Skin Rash | If a penicillin indicated: amoxicillin oral challenge<br>Any cephalosporin safe |
| Severe Cutaneous Adverse Reaction<br>SJS/TEN, DRESS, AGEP | Avoid β-lactams |
| Antibody mediated<br>(*Hemolytic anemia, neutropenia, thrombocytopenia*)<br>Immune-complex<br>(*vasculitis, serum sickness*)<br>Cell-mediated<br>(*Interstitial nephritis, drug-induced liver injury*) | No available testing<br>In general, when severe avoid β-lactams |

20

**OL9 Penicillin Allergy**

*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## Question #3

A 35-year-old healthy woman presents to your primary care clinic with sore throat and fever. Two of her school-age children were recently diagnosed with strep throat.

On exam, she is afebrile. She has pharyngeal erythema, tonsillar exudate, and bilateral cervical lymphadenopathy.

Rapid Group A streptococcal testing is positive.

She has a history of penicillin allergy that occurred when she was a child. She has no direct recall of the reaction. She has not to her knowledge received penicillins or cephalosporins since.



## Question #3

### What do you do advise?

A. Prescribe amoxicillin with monitored first dose
B. Prescribe clindamycin
C. Prescribe cephalexin
D. Prescribe azithromycin
E. Urgent referral to allergy clinic



## Question #3

### What do you do advise?

**A. Prescribe amoxicillin with monitored first dose**
B. Prescribe clindamycin
C. Prescribe cephalexin
D. Prescribe azithromycin
E. Urgent referral to allergy clinic



## Clinical Decision tools

Designed to identify low risk penicillin allergies

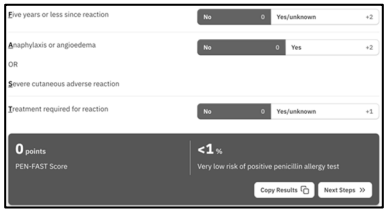
Clinical features:

- **F** ive or fewer years since the reaction (2 points)
- **A** naphylaxis or angioedema OR
  **S** evere cutaneous adverse reaction (2 points)
- **T** reatment required for reaction (1 point)

Risk of positive allergy test:

- 0-2 points: low risk ⇨ Oral challenge
- ≥ 3 points: additional triage

PEN-FAST Tool




https://www.mdcalc.com/calc/10422/penicillin-allergy-decision-rule-pen-fast



**OL9 Penicillin Allergy**
*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## Question #4

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.



## Question #4

### What do you do counsel?

A. Administer clindamycin
B. Administer cefazolin
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin



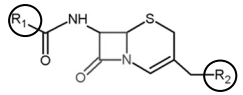
## Question #4

### What do you do counsel?

A. Administer clindamycin
**B. Administer cefazolin**
C. Administer cefazolin after intraoperative test dose
D. Administer ceftriaxone
E. Administer vancomycin



## Cephalosporin Allergy




- Allergy arises from side chains
- 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, Loracarbef |
| Cefepime, Ceftriaxone, Cefotaxime, Cefpodoxime, Cefuroxime |
| Ceftazidime, Cefiderocol, Aztreonam |

- Avoid cephalosporins if SCAR to cephalosporin

https://adsp.nm.org/allergy-resources.html



**OL9 Penicillin Allergy**
*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

## 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
- Cefaclor is associated with serum sickness reaction in children
  - Does not predict cross reactivity with penicillin or other cephalosporins

29

## A Few More Testable Points

- 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

30

## Thank you and good luck!



*"The penicillin looks good."*

31

**OL9 Penicillin Allergy**

*Speaker: Sandra Nelson, MD*

©2026 Infectious Disease Board Review, LLC

**Online Only Lectures**

---

**OL10**

# Immunomodulatory Agents: What Can Be Tested

**Jennifer Saullo, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Immunomodulatory Agents: What Can Be Tested

**Jennifer Saullo, MD, PharmD, FIDSA**
**Duke University Medical Center**

5/29/26




## Disclosures of Financial Relationships with Relevant Commercial Interests

- Royalties from UpToDate

## General Principles

*Immunomodulatory Agents*

- **Why important**
  - Rapidly expanding therapeutics and applications
  - Mechanism of action => immune defect => distinct infection risks
- **High-yield board concepts**
  - Identify the immune deficit
  - Recognize classic infection associations
  - Known relevant screening and prophylaxis
  - Understand vaccine needs → timing, types, and contraindications
  - Recognize mimics → immunomodulatory toxicities vs underlying disease(s) vs infection
  - Be cognizant of FDA black-box warnings

## Key Immunomodulatory Agents*

- Lymphoid-cell targeted monoclonal antibodies (anti-CD20, anti-CD52)
- Tumor necrosis factor (TNF)-alpha inhibitors
- Janus kinase (JAK) inhibitors
- Interleukin (IL) inhibitors (IL-6 and IL-17 inhibitors)
- Complement inhibitors
- Sphingosine-1-phosphate (S1P) receptor modulators
- Immune checkpoint inhibitors (CTLA-4, PD-1, PD-L1 and LAG-3)
- Integrin inhibitors (natalizumab)
- Bruton tyrosine kinase inhibitors

**Note: CAR T-cell and Bispecific T-cell engager therapies discussed separately in the Infections in Neutropenic Cancer Patients Lecture; Lists of Agents/Clinical Uses are not exhaustive*


© 2026 Infectious Disease Board Review

## General Principles
*Immunomodulatory Therapies*

**SCREENING TESTS**

- Viral hepatitis (B and C)
- Human immunodeficiency Virus (HIV)
- Latent tuberculosis
- Other geographic considerations
  - Endemic fungi
  - Strongyloides

**VACCINATIONS**

- Ensure up-to-date
- Relevant for age and therapy
- Timing pre-therapy
  - Inactivated @ least 2 weeks
  - Live, attenuated @ least 4 weeks
- Contraindications - live vaccines

**KEY POINT TO REMEMBER: infection risks depend on multiple factors - age, geographic residence, comorbidities, preceding and concomitant immunosuppressive and immunomodulatory therapies, and time on therapy**

## Question #1

68-year-old man, originally from Taiwan, with underlying follicular lymphoma, plans to initiate single-agent **rituximab** therapy.

Which of the baseline serologies would be **most important** when assessing infectious risks and the relevant need for prophylaxis with rituximab therapy?

A. Cytomegalovirus
B. Toxoplasmosis
C. Hepatitis A
D. Hepatitis B
E. Hepatitis C

## Question #1

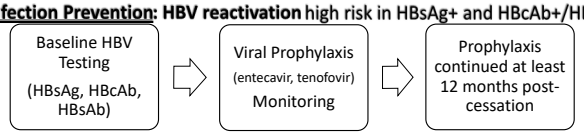
68-year-old man, originally from Taiwan, with underlying follicular lymphoma, plans to initiate single-agent **rituximab** therapy.

Which of the baseline serologies would be **most important** when assessing infectious risks and the relevant need for prophylaxis with rituximab therapy?

A. Cytomegalovirus
B. Toxoplasmosis
C. Hepatitis A
D. Hepatitis B
E. Hepatitis C

## Lymphoid-cell Targeted Monoclonal Antibodies
*Anti-CD20 Monoclonal Antibodies*

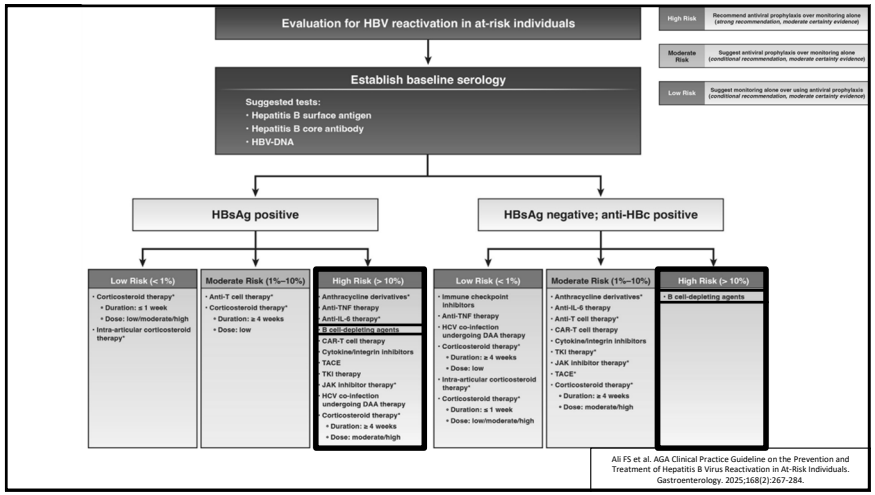
- **Agents: *Rituximab*;** others: *obinutuzumab, ocrelizumab,* and *ofatumumab*
- **Uses:** broad - oncologic, autoimmune/inflammatory, hematologic (non-malignant), neurologic, renal, and transplant medicine
- **Infection risks:** prolonged B-cell depletion, hypogammaglobulinemia, and late-onset neutropenia (weeks to months post-exposure)
  - Appreciable impairment in vaccine response (@ least 6-12 months post-use), no LIVE vaccines
  - **Infection Prevention: HBV reactivation** high risk in HBsAg+ and HBcAb+/HBsAg-




  - Other viruses (herpesvirus, JC virus and PML)
  - *Pneumocystis jirovecii* infection

Hwang JP et al. J Clin Oncol. 2020;38(31):3698.
Tétrault NA et al. Hepatology. 2018;67(4):1560.

**OL10 Immunomodulatory Agents: What Can Be Tested**
*Jennifer Saullo, MD, PharmD, FIDSA*
© 2026 Infectious Disease Board Review




Ali FS et al. AGA Clinical Practice Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation in At-Risk Individuals. Gastroenterology. 2025;168(2):267-284.

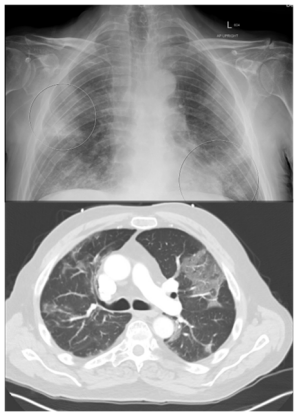
## Question #2

63-year-old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside preemptive therapy for CMV. Serial plasma CMV PCR testing has been negative to-date.

Presents with a several-week history of slowly progressing shortness of breath and new low-grade non-neutropenic fevers. CXR followed by cross-sectional chest images are shown (R).

This presentation is likely due to the **lack of** which of the following recommended prophylactic therapies?

A. Letermovir
B. Valganciclovir
C. Entecavir
D. Levofloxacin
E. Sulfamethoxazole-Trimethoprim



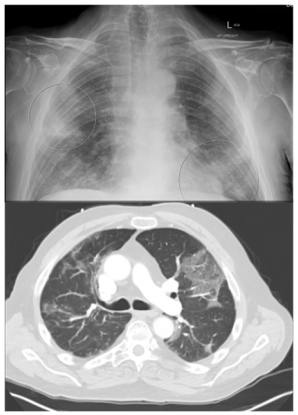
## Question #2

63-year-old man with T-cell prolymphocytic leukemia on single-agent **alemtuzumab** therapy. Receiving acyclovir prophylaxis (for HSV/VZV) alongside preemptive therapy for CMV. Serial plasma CMV PCR testing has been negative to-date.

Presents with a several-week history of slowly progressing shortness of breath and new low-grade non-neutropenic fevers. CXR followed by cross-sectional chest images are shown (R).

This presentation is likely due to the **lack of** which of the following recommended prophylactic therapies?

A. Letermovir
B. Valganciclovir
C. Entecavir
D. Levofloxacin
E. Sulfamethoxazole-Trimethoprim



## Lymphoid-cell Targeted Monoclonal Antibodies
### *Anti-CD52 Monoclonal Antibodies*

- **Agent: *Alemtuzumab* -** anti-CD52 Mab, present on B- and T lymphocytes, macrophages, and NK cells
- **Uses**: broad - oncology/hematology (e.g., CLL, T-PLL), transplant medicine, and autoimmune diseases
- **Infection risks:** due to prolonged B- and T-cell depletion, cytopenias
  - Viral infections - especially herpesvirus (e.g. ***CMV***, VZV, HSV), hepatitis B/C, rare JCV PML
  - Mycobacterial and **fungal infections** (e.g. **PJP**, *Aspergillus*)
  - Bacterial infections, including *Listeria monocytogenes*
- **Infection prevention:**
  - **Viral and PJP prophylaxis –** minimum 2 months after alemtuzumab and CD4 ≥ 200 cells/mcL
  - **Pre-emptive CMV monitoring –** minimum 2 months after alemtuzumab
  - Impaired vaccine response, no LIVE vaccines

**OL10 Immunomodulatory Agents: What Can Be Tested**

*Jennifer Saullo, MD, PharmD, FIDSA*

© 2026 Infectious Disease Board Review

## Question #3

A 35-year-old woman with refractory Crohn's disease is to scheduled to begin infliximab. She emigrated from India to the United States at age 14 and has no prior documented tuberculosis (TB) screening or TB infection.

She is currently well, without fevers, chronic cough, or other constitutional symptoms. An interferon-gamma release assay (IGRA) returns positive. What is the most appropriate next best step?

A. Cancel planned infliximab therapy and treat for active tuberculosis infection
B. Delay infliximab, obtain chest imaging and sputum AFB cultures, and if imaging normal, begin infliximab
C. No additional evaluation required, begin infliximab now
D. Delay infliximab, obtain chest imaging, and if normal, start latent TB therapy, then begin infliximab
E. Delay infliximab, obtain chest imaging, and if normal, complete a full course of latent TB therapy before starting infliximab


## Question #3

A 35-year-old woman with refractory Crohn's disease is to scheduled to begin infliximab. She emigrated from India to the United States at age 14 and has no prior documented tuberculosis (TB) screening or TB infection.

She is currently well, without fevers, chronic cough, or other constitutional symptoms. An interferon-gamma release assay (IGRA) returns positive. What is the most appropriate next best step?

A. Cancel planned infliximab therapy and treat for active tuberculosis infection
B. Delay infliximab, obtain chest imaging and sputum AFB cultures, and if imaging normal, begin infliximab
C. No additional evaluation required, begin infliximab now
D. Delay infliximab, obtain chest imaging, and if normal, start latent TB therapy, then begin infliximab
E. Delay infliximab, obtain chest imaging, and if normal, complete a full course of latent TB therapy before starting infliximab


## Tumor Necrosis Factor (TNF)-Alpha Inhibitors

- **Agents**: **infliximab**, adalimumab, etanercept, certolizumab pegol, and golimumab
  - All are monoclonal Abs, except etanercept, a soluble receptor fusion protein
- **Uses**: autoimmune and inflammatory conditions (e.g., rheumatoid/psoriatic arthritis, inflammatory bowel disease)
- **Mechanism of Action/Immune defects**:

  TNF-α is important for
  - **Formation and maintenance of granulomas**
  - Development of phagosomes
  - Activation and differentiation of macrophages
  - Immune response against viral pathogens

Baddley JW et al. Clin Microbiol Infect. 2018;24 Suppl 2:S10-S20. PMID: 29459143.

## Tumor Necrosis Factor (TNF) Alpha Inhibitors
### *Infection Risks*

- **Bacterial infections**
  - Including *Legionella, Listeria, Nocardia, Actinomyces, Salmonella*
  - *Tropheryma whipplei* (seronegative arthropathy->exacerbation of undiagnosed, subclinical Whipple's disease)
- **Mycobacterial infections**: including tuberculosis and non-tuberculous mycobacteria
  - **TB screening in ALL patients**

**Screening:** History, Exam, Imaging + IGRA>TST ⇨ **Screen POSITIVE:** -Rule out active TB -Initiate LTBI tx ⇨ **Timeline for LTBI:** PRIOR to TNF-α inhibitor start*

**Guidelines recommend at least 1-3 weeks of LTBI therapy, do not need to complete prior to start*

- **Viral hepatitis -** hepatitis B and C; (HBsAg+ high risk, HBsAg-/HBcAb+ lower risk)
- **Fungal infections**
  - ***Endemic fungi* (histoplasmosis**, blastomycosis, coccidioidomycosis)
  - Aspergillosis, PJP
- **Parasitic infections -** including Leishmaniasis
- **Vaccination status** - update prior to start, no LIVE vaccines

Mimics
-Heart failure
-Demyelinating disease
-Malignancies


© 2026 Infectious Disease Board Review

## Question #4

What is the most effective first-line prevention strategy for the most common viral infection in patients who are initiating tofacitinib therapy for rheumatoid arthritis?

A. Pre-emptive monitoring with weekly cytomegalovirus plasma PCR
B. Acyclovir prophylaxis
C. Valganciclovir prophylaxis
D. Shingles (recombinant zoster) vaccination
E. Regularly scheduled intravenous immune globulin (IVIG)

## Question #4

What is the most effective first-line prevention strategy for the most common viral infection in patients who are initiating tofacitinib therapy for rheumatoid arthritis?

A. Pre-emptive monitoring with weekly cytomegalovirus plasma PCR
B. Acyclovir prophylaxis
C. Valganciclovir prophylaxis
D. **Shingles (recombinant zoster) vaccination**
E. Regularly scheduled intravenous immune globulin (IVIG)

## Janus-Kinase Inhibitors

**AGENTS and USES**

- **Autoimmune/inflammatory disease JAK inhibitors** (e.g., rheumatoid and psoriatic arthritis, Crohn's disease, ulcerative colitis, atopic dermatitis, giant cell arteritis)
  - Tofacitinib – JAK1/JAK3
  - Baricitinib - JAK1/JAK2
  - Upadacitinib and Abrocitinib - JAK1-selective
- **Hematology-Oncology JAK inhibitors** [e.g., myelo, myelofibrosis, polycythemia vera, graft-versus-host disease (GVHD)]
  - Ruxolitinib – JAK1/JAK2
  - Fedratinib – JAK2-selective, used for myelofibrosis

**MECHANISM/IMMUNE DEFECTS**

- Inhibition of JAK-STAT pathways
  - Reduced cytokine production
  - Reduced immune cell development
  - Cytopenias (JAK2 inhibition)
- Impact on both innate and adaptive immunity

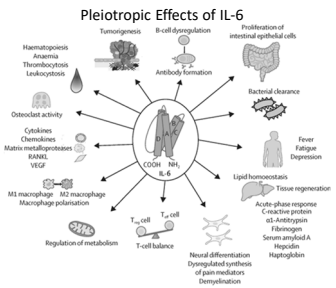
## Janus-Kinase Inhibitors
### *Infection Risks*

- Black box warning - bacterial, fungal, viral, and other OIs
- **Bacterial infections** - severe pneumonia/bronchitis, UTI, cellulitis
- **Viral infections**
  - **Herpes zoster reactivation – most common**
  - Other herpes virus, including HSV, CMV; rare JCV – PML
  - Viral hepatitis - HBV, HCV; HBsAg+ high risk, HBsAg-/HBcAb+ moderate risk
- **Fungal infections**
  - PJP (consider concomitant IST for prophylaxis considerations)
  - Endemic fungi (geographic history)
- **Mycobacterial infections** – TB, pre-transplant screening essential


© 2026 Infectious Disease Board Review

## Interleukin-6 Inhibitors

- **Agents**:
  - **Tocilizumab** – monoclonal Ab targeting IL-6 receptor (others: sarilumab and satralizumab)
  - Siiltuximab – targets IL-6
- **Uses: (tocilizumab, including off-label):** rheumatoid arthritis, giant cell arteritis, COVID-19, cytokine release syndrome (CRS), neuromyelitis optica, Takayasu arteritis
- **Mechanism/immune defect**:
  - IL-6 best known for **pro-inflammatory effects** *(trans-signaling pathway involving gp130)*
  - Pleiotropic cytokine – anti-inflammatory, pro-resolution, and regenerative properties, **important for pathogen clearance** *(classic signaling pathway)*
  - mAbs do not discriminate between pathways – impacts on acute phase responses, neutrophil trafficking, B-cell maturation, and T-cell differentiation




McElvaney OJ et al. Lancet Respir Med. 2021;9(6):643-654. PMID: 33872590.

## Interleukin-6 Inhibitors
### *Infection Risks*

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

## Question #5

A 55-year-old female started a new therapy for psoriasis 3 months ago. She presents with recurrent oral pain and tenderness alongside white plaques on the tongue and palate.

Which of the following was the most likely agent she was started on?

A. Acitretin
B. Cyclosporine
C. Infliximab
D. Etanercept
E. Bimekizumab

## Question #5

A 55-year-old female started a new therapy for psoriasis 3 months ago and presents with recurrent oral pain and tenderness alongside white plaques on the tongue and palate.

Which of the following was the most likely agent she was started on?

A. Acitretin
B. Cyclosporine
C. Infliximab
D. Etanercept
E. Bimekizumab


© 2026 Infectious Disease Board Review

## IL-17 Inhibitors

- **Agents:**
  - Monoclonal Abs targeting IL-17
  - Bimekizumab (dual IL-17A/IL17-F), ixekizumab (IL-17A), and secukinumab (IL-17A)
- **Uses:** autoimmune and inflammatory diseases – including psoriasis, ankylosing spondyloarthritis, hidradenitis suppurativa
- **Mechanism/immune defects:** reduces neutrophil recruitment and antimicrobial peptide production at mucosal/skin surfaces + gut epithelial barrier protection

## IL-17 Inhibitors
### *Infection Risks*

- **Candidiasis –** oral, vaginal, typically mild-moderate, responsive to topical/oral antifungals
- **Bacterial infections –** primarily respiratory tract infections
- **Mycobacterial infections** – TB risk low overall, labeling still recommends screening*
- **Viral –** herpes viruses (HSV, VZV), hepatitis B/C screening; overall lower rates of HBV infection/reactivation
- **Other OIs –** uncommon
- **Potential mimic for inflammatory bowel disease (IBD)** – do not use in patients with active IBD, can cause new-onset or exacerbation of IBD

*Blauvelt A et al. Joint position statement from National Psoriasis Foundation Medical Board and the International Psoriasis Council on routine testing for latent tuberculosis infection prior to and during treatment of psoriasis patients with interleukin 17 or interleukin 23 inhibitors. J Am Acad Dermatol. 2026;94(3):802-809.

## Question #6

A 35-year-old female presents with fevers, headache, confusion, and a diffuse petechial rash. Four months ago, she was diagnosed with paroxysmal nocturnal hemoglobinuria after evaluation for abdominal pain, dark urine, hemolytic anemia, and portal vein thrombosis. She was started on eculizumab with improvement in symptoms.

On examination, temperature is 39.4°C (102.9°F), blood pressure is 86/52 mm Hg, and neck stiffness is present. Blood cultures grow gram-negative diplococci.

This patient's infection is most likely due to impaired:

A. Neutrophil respiratory burst
B. Terminal complement-mediated bacterial lysis
C. Interleukin-6 activity
D. Interleukin-17 activity
E. C3b-mediated opsonization

## Question #6

A 35-year-old female presents with fevers, headache, confusion, and a diffuse petechial rash. Four months ago, she was diagnosed with paroxysmal nocturnal hemoglobinuria after evaluation for abdominal pain, dark urine, hemolytic anemia, and portal vein thrombosis. She was started on eculizumab with improvement in symptoms.

On examination, temperature is 39.4°C (102.9°F), blood pressure is 86/52 mm Hg, and neck stiffness is present. Blood cultures grow gram-negative diplococci.

This patient's infection is most likely due to impaired:

A. Neutrophil respiratory burst
B. Terminal complement-mediated bacterial lysis
C. Interleukin-6 activity
D. Interleukin-17 activity
E. C3b-mediated opsonization

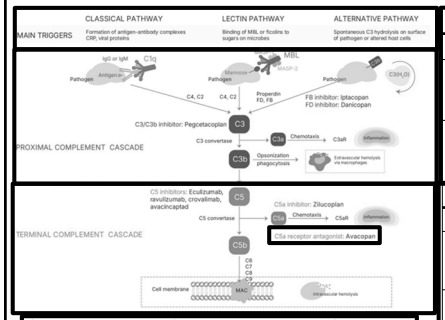

© 2026 Infectious Disease Board Review

## Complement Inhibitors

- **Agents:**
  - mAbs (eg, eculizumab, ravulizumab, and crovalimab)
  - Peptides/macrocycles (eg, pegcetacoplan and zilucoplan)
  - Small molecule inhibitors (eg, avacopan, danicopan, and iptacopan)

- **Uses:** paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized myasthenia gravis (gMG), neuromyelitis optica spectrum disorder (NMOSD), C3 glomerulopathy, immune complex–mediated membranoproliferative glomerulonephritis (IC-MPGN), IgA Nephropathy, and ANCA-associated vasculitis

## Complement Inhibitors
### *Mechanism/Immune Defects*




| PROXIMAL Cascade Inhibition | |
|---|---|
| **Targets** | C3, Factor B, Factor D |
| **Therapies** | C3/C3b inhibitor: pegcetacopan<br>FB inhibitor: ipacopan<br>FD inhibitor: danicopan |
| **Infection Risk** | Susceptibility to encapsulated bacteria, including *Neisseria*, *Streptococcus pneumoniae*, *Haemophilus influenzae* |

| TERMINAL Cascade Inhibition | |
|---|---|
| **Targets** | C5, C5a, or C5-C9 assembly |
| **Therapies** | C5 inhibitors: eculizumab, ravulizumab (mAb)<br>C5a inhibitor: zilucoplan<br>*C5a receptor antagonist: avacopan** |
| **Infection Risk* (for C5/C5a inhibitors only)** | -Markedly increased risk of *N. meningitidis* and other *Neisseria* spp<br>-Some increased risk for *H. influenzae* and *Moraxella catarrhalis*<br>-Encapsulated bacteria risk theoretically less than proximal inhibition |

*Note that **avacopan** (C5a receptor antagonist) preserves MAC formation and does not carry meningococcal risk

Subramanian AK et al. Clin Infect Dis. 2026; PMID: 41711415

## Complement Inhibitors
### *Infection Prevention*

- ***Neisseria* infections**
  - Meningococcal ACWY (quadrivalent) and B serogroup vaccines – initial series and boosters
    - At least 2 weeks prior to therapy start
    - If unable, antibiotic prophylaxis at least 2 weeks post-vaccination
    - Many experts continue antibiotic prophylaxis for duration of complement inhibitor therapy – *current practice is provider-dependent*
  - Recognize pre-treatment risks for **gonorrhea infection and test**
  - **Vaccination + antibiotic prophylaxis will not prevent all cases**
    - Non-vaccine-covered strains
    - Inadequate response to vaccine
    - Antimicrobial resistance
- **Other encapsulated bacteria** – ensure pneumococcal and *H. influenzae* vaccinations are also up-to-date, particularly with proximal complement inhibitors
- Education paramount – signs/symptoms of infection, when to seek immediate attention

## Sphingosine-1-phosphate (S1P) Receptor Modulators

- **Agents:** fingolimod, siponomod, ozanimod, and ponesimod
- **Uses**: multiple sclerosis, ulcerative colitis
- **Mechanism/Immune Defects**
  - Binds to S1P receptor on lymphocyte → receptor internalized → lymphocytes unable to follow S1P gradient to egress from lymph nodes
  - Essentially **sequesters lymphocytes in the lymph nodes**
- **Infection risks**
  - Bacterial (respiratory tract, skin/soft tissue, UTI)
  - **Viral (most common *VZV, including disseminated, *HSV**; rare PML – late onset 18 + months )
  - Fungal infections, including cryptococcus
  - Mycobacterial infections
- Potential mimics (PRES, hepatotoxicity, bradycardia)
- **Infection Prevention: VZV Ab screening – if seronegative, vaccinate (complete 1 month before start); recombinant zoster vaccine in immune patients**

McGinley MP, Cohen JA. Lancet. 2021 Sep;398(10306):1184-1194. PMID: 34175020.


© 2026 Infectious Disease Board Review

## Question #7

A 35-year-old woman with relapsing remitting multiple sclerosis has been receiving natalizumab for 20 months.

Which of the following are not considered relevant for risk estimation for Progressive Multifocal Leukoencephalopathy (PML) to guide decisions regarding use of natalizumab therapy?

A. JCV antibody status
B. History of prior immunosuppressive therapies
C. Duration of natalizumab therapy
D. JCV antibody index
E. JCV plasma PCR

## Question #7

A 35-year-old woman with relapsing remitting multiple sclerosis has been receiving natalizumab for 20 months.

Which of the following are not considered relevant for risk estimation for Progressive Multifocal Leukoencephalopathy (PML) to guide decisions regarding use of natalizumab therapy?

A. JCV antibody status
B. History of prior immunosuppressive therapies
C. Duration of natalizumab therapy
D. JCV antibody index
E. JCV plasma PCR

## Integrin Inhibitors
*Natalizumab*

**Mechanism of action/immune defects**

- Humanized IgG4 monoclonal antibody targeting the **α4 subunit of integrin**
  - Blocks T-cell, B-cell, and monocyte trafficking, adhesion and migration across the **blood-brain barrier**
  - Also binds MadCAm-1 on **gut endothelium**, decreasing migration of memory T cells.

**Special Mention: differentiation of risk for integrin inhibitors**

| Agent | Target | Indication | High Yield Board Buzz |
|---|---|---|---|
| **Natalizumab** | α4 integrin | Multiple sclerosis, Crohn | PML – PML – PML |
| Vedolizumab* | α4β7 integrin | Ulcerative colitis, Crohn | Lower risk of infection |

*decreases migration of memory T cells to GI tract only, as opposed to the CNS (natalizumab)

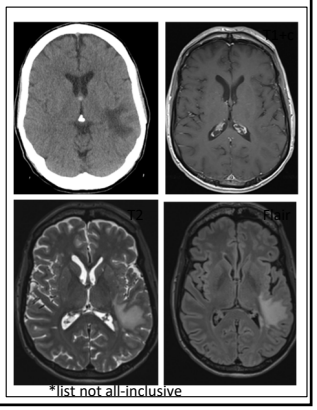
## Natalizumab
***Infection Risks***

- **JCV-associated progressive multifocal leukoencephalopathy**
- Herpesvirus infection
  - HSV, VZV
  - Particularly meningitis/encephalitis
  - Acute retinal necrosis
- General infection and opportunistic infections reported, often dependent on concomitant therapeutics


© 2026 Infectious Disease Board Review

## Progressive Multifocal Leukoencephalopathy (PML)

- Demyelinating CNS infection – associated with JC virus
- **Risk factors – presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants**
- Risk management program enrollment is required for use
- Clinical presentation
  - With close monitoring → goal is early detection when asymptomatic
  - Symptoms – progressive, subacute neurological deficits with cognitive impairment, limb and gait ataxia, weakness, visual changes, hemiparesis, aphasia
- Diagnostics - CNS imaging (*asymmetry, periventricular/subcortical, non-contrast enhancing, spares grey matter), CSF PCR, brain biopsy
- Treatment - no effective treatment; immune restoration key; immediate cessation of therapy and plasma exchange transfusion (PLEX) considered for removal of drug
- Risk for post-cessation immune reconstitution inflammatory syndrome (IRIS)



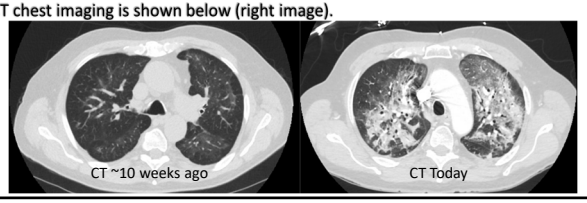

*list not all-inclusive

## Question #8

A 54-year-old man with metastatic non-small cell lung cancer (NSCLC) on 3 months of combination therapy with nivolumab and ipilimumab presented with several weeks of progressing dyspnea and cough. CT chest showed diffuse ground-glass opacities (bottom left image). He was diagnosed with grade-2 immune checkpoint inhibitor-related pneumonitis. Prednisone 1mg/kg/day initiated with relatively rapid improvement. Plans were made for a slow steroid taper.

He now presents 8 weeks into his steroid taper (current dose: prednisone 30mg/day) with recurrent cough, dyspnea, new fevers to 38.6°C, and marked fatigue.

- Laboratory studies show a WBC of 12,000/µL with lymphopenia (absolute lymphocyte count 300/µL) and normal hepatic and renal indices.
- Repeat CT chest imaging is shown below (right image).




## Question #8 (continued)

Which of the following is the most appropriate next step?

A. Resume oral prednisone at 2mg/kg/day
B. Add infliximab 5mg/kg intravenous therapy
C. Add mycophenolate mofetil 1 g twice daily
D. Add trimethoprim-sulfamethoxazole (TMP-SMX) double strength three times weekly
E. Perform bronchoscopy with bronchoalveolar lavage (BAL) for bacterial, fungal, and AFB cultures, and PJP PCR

## Question #8 (continued)

Which of the following is the most appropriate next step?

A. Resume oral prednisone at 2mg/kg/day
B. Add infliximab 5mg/kg intravenous therapy
C. Add mycophenolate mofetil 1 g twice daily
D. Add trimethoprim-sulfamethoxazole (TMP-SMX) double strength three times weekly
E. Perform bronchoscopy with bronchoalveolar lavage (BAL) for bacterial, fungal, and AFB cultures, and PJP PCR


© 2026 Infectious Disease Board Review

## Checkpoint Inhibitors

❖ **Agents**

| Target | Example |
|---|---|
| PD-1 | Pembrolizumab**, nivolumab**, cemiplimab |
| PD-L1 | Atezolizumab, durvalumab, avelumab |
| CTLA-4 | **Ipilimumab**, tremelimumab |
| LAG-3 | Relatlimib (with nivolumab) |

CTLA-4 ,cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed cell death protein 1, PD-L1, programmed death-ligand 1; LAG-3, lymphocyte activation gene 3.

❖ **Uses:** melanoma, solid tumors (e.g., **NSCLC**, RCC, HCC, Bladder Ca), SCC, certain lymphomas

❖ Mechanism
- Target CTLA-4, PD-1, PD-L1 and LAG-3
- Block inhibitory receptors/ligands used by tumors to evade immune surveillance
- Result = **immune activation *(not immunosuppression)***

❖ Immune-Related Adverse Effects (irAEs)
- Autoimmune phenomena
- Can affect any organ system (lungs, GI, skin, endocrine, kidney, CNS, etc)
- Moderate-severe: require IST
  - Typically steroids
  - If refractory, other IST applied (e.g., TNF alpha inhibitors, mycophenolate)

❖ Highly testable
- **Infectious mimics**
- **Infectious complications**
  - Application of IST
  - Dysregulated immunity

| Presentation | irAEs of Checkpoint Inhibitors | Infectious Considerations |
|---|---|---|
| Wasting / Asthenia | Hypo-/hyperthyroidism, diabetes, hypophysitis, adrenal insufficiency | Endocarditis, PML, sepsis, colitis, chronic infections (syphilis, viral), thrush |
| Skin | Maculopapular rash, pruritus, vitiligo, autoimmune (pemphigus, eczema, psoriasis), vasculitis | Sepsis (candidemia, bacteremia), septic emboli (*Staphylococcus, Pseudomonas, Fusarium*), shingles, herpes simplex, cellulitis |
| Pulmonary | Pneumonitis (and organizing pneumonitis), sarcoidosis, interstitial fibrosis, pericarditis, myocarditis | Pneumonia involving bacteria, fungal (PJP, *Aspergillus*), viral (CMV, community respiratory), mycobacterial pathogens |
| Gastrointestinal including hepatic | Oral mucositis, enterocolitis, pancreatitis, perforation, hepatitis, cholangitis (primary biliary cholangitis) | Thrush, *Clostridium difficile* colitis, enteric pathogens and parasites, viral (norovirus, CMV), perforation, peritonitis, hepatitis viruses (ABCE), adenovirus, leptospirosis, mycobacteria |
| Headaches, confusion | Hypophysitis (pituitary enlargement), immune reconstitution, vasculitis (stroke), PRES, hypo-/hyperthyroidism, | Meningitis (bacterial, viral, *Cryptococcus*), encephalitis (HSV/VZV), endocarditis with septic embolus, abscess (*Aspergillus*) |

Adapted from: Fishman JA et al. CID 2019 Clin Infect Dis. 2019;69(6):909-920. PMID: 30520987.

**Additional Testable Concepts:**
1) Opportunistic infections occur due to **immunosuppressive treatment** of IRAEs (e.g., steroids and PJP pneumonia) and/or **dysregulated immunity pathways (**e.g., latent TB or inflammatory TB presentations, viral reactivation); 2) Checkpoint inhibitors can cause cytokine release syndrome (*less common*)

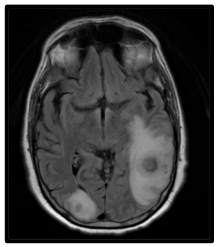
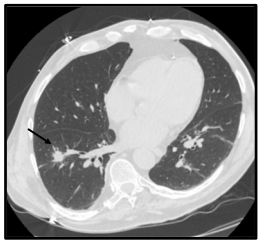
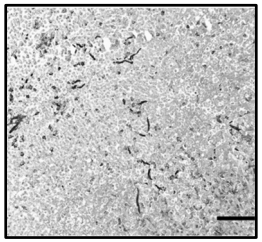
## Bruton's Tyrosine Kinase (BTK) Inhibitors

**Patient**: 62-year-old man, underlying CLL on **single-agent ibrutinib** x 4 months

**Presentation:** fevers, confusion, dysarthria with significant word finding difficulties

**Imaging:** brain MRI + chest CT

**Histopathology:** brain biopsy

## Bruton's Tyrosine Kinase (BTK) Inhibitors

- **Agents**: include - **Ibrutinib**, Acalabrutinib, Zanubrutinib
- **Uses**: most commonly applied in CLL, lymphoma
- **Mechanism/Immune defects**: key enzyme in B-cell receptor signaling→ block downstream activation of B-cell receptor pathway, cell growth, macrophage function
- **Infectious risks**
  - Bacterial infections (most common)
  - Opportunistic fungal infections, inclusive of CNS involvement (e.g. *Aspergillus, Cryptococcus*, PJP)
- **Infection prevention**
  - Consider fungal (mold, PJP) and HSV/VZV prophylaxis if additional risk factors (inclusive of concomitant therapies)

Shah M et al. Transpl Infect Dis. 2024:e14283.

# OL10 Immunomodulatory Agents: What Can Be Tested

*Jennifer Saullo, MD, PharmD, FIDSA*

© 2026 Infectious Disease Board Review

| Immunomodulatory Therapy | Examples | Board Buzz - Infection Risk |
|---|---|---|
| CD20 inhibitors | Rituximab, obintuzumab | Hepatitis B reactivation, impaired vaccine response, hypogammaglobulinemia, rare JCV PML |
| CD52 inhibitors | Alemtuzumab | PJP, CMV, HSV/VZV, other invasive fungal and opportunistic infections |
| TNF-alpha inhibitors | Infliximab, adalimumab | Tuberculosis, endemic fungi, other intracellular pathogens |
| Janus kinase inhibitors | Tofacitinib, ruxolitinib | Herpes zoster, TB, other opportunists |
| Interleukin-6 inhibitors | Tocilizumab, sarilumab | Severe infections, masked infectious signs/symptoms – normal CRP, GI perforation |
| Interleukin-17 inhibitors | Bimekizumab, secukinumab | Mucocutaneous candidiasis |
| Complement inhibitors | Eculizumab, ravulizumab | Severe/disseminated *Neisseria meningitis*, Gonococcal infections, other encapsulated bacteremia (Pneumococcus, *H. influenzae*) |
| Sphingosine 1-phosphate receptor modulators | Fingolimod, Siponimod | VZV infections, other viral infections (HSV, rare CMV, JCV-associated PML) |
| Integrin inhibitors | Natalizumab | PML (JC Virus) |
| Checkpoint inhibitors | Pembrolizumab, nivolumab, ipilimumab | PJP when treated for iRAEs and no prophylaxis, mimics from iRAEs (pneumonitis, colitis) |
| Bruton's tyrosine kinase inhibitors | Ibrutinib, acalabrutinib | Invasive fungal infections (aspergillosis, cryptococcosis), including CNS involvement/dissemination |

## Questions / Comments

E-mail contact: jennifer.horan@duke.edu

**OL10 Immunomodulatory Agents: What Can Be Tested**

*Jennifer Saullo, MD, PharmD, FIDSA*

© 2026 Infectious Disease Board Review

OL11

# Treating Antimicrobial Resistant Infections III Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia

Pranita Tamma, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Antimicrobial Resistant Infections III
# *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*

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

## 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*

## Disclosures

- I have no disclosures.

*Clinical Infectious Diseases*
IDSA GUIDELINES

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:

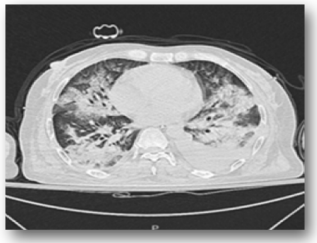
- Extended-spectrum beta-lactamase producing Enterobacterales (ESBL-E)
- AmpC beta-lactamase producing Enterobacterales (AmpC-E)
- Carbapenem-resistant Enterobacterales
- *Pseudomonas aeruginosa* with difficult-to-treat resistance
- Carbapenem-resistant *Acinetobacter baumannii* complex
- *Stenotrophomonas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

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


©2026 Infectious Disease Board Review, LLC

## 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
- *P. aeruginosa* recovered from bronchoalveolar lavage fluid



| 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 |
| Imipenem | 8 µg/mL | R |
| Meropenem | 8 µg/mL | R |
| Piperacillin/tazobactam | > 64/4 µg/mL | R |
| Tobramycin | > 8 µg/mL | R |

Clinical and Laboratory Standards Institute (CLSI) has **no susceptible category** for polymyxins against *P. aeruginosa* (≤2 µg/mL = intermediate)

## Colistin is No Longer a Preferred Therapy

- Penetration into pulmonary epithelial lining fluid is suboptimal, even with dose optimization
- Colistin administered as inactive prodrug colistin methanesulfonate, which is slowly and incompletely converted to colistin **(<10%)**
  - Difficult to achieve adequate colistin plasma concentrations in patients with normal renal function
- Many reports of heteroresistance during polymyxin monotherapy
  - May be related to suboptimal polymyxin concentrations at site of infection
- Many new antibiotic trials use colistin as a comparator; almost all with inferior outcomes in the colistin arm
- Almost half of patients receiving colistin develop acute kidney injury

Landersdorfer CB, et al. J Antimicrob Chemother. 2018;73462-468. Cheah S, et al. J Antimicrob Chemother. 2015;70:3291-7. Sandi AM, et al. Clin Infect Dis. 2013;57:524-31. Li J, et al. Antimicrob Agents Chemother. 2006;9:2946–50. Rojas LJ, et al. Clin Infect Dis. 2016;64:711–718. Howard-Anderson J, J Antimicrob Chemother. 2022; 77:793-798.

| General Mechanisms | Examples | Antibiotics Typically Impacted |
|---|---|---|
| Reduced membrane permeability | Reduced production of OprD porin | Carbapenems (imipenem>meropenem) |


©2026 Infectious Disease Board Review, LLC

| General Mechanisms | Examples | Antibiotics Typically Impacted |
|---|---|---|
| Reduced membrane permeability | Reduced production of OprD porin | Carbapenems (imipenem>meropenem) |
| Active antibiotic extrusion | Increased expression of MexAB-OprM efflux pump | Piperacillin, cefepime, meropenem, fluoroquinolones, tazobactam, avibactam, relebactam |

| General Mechanisms | Examples | Antibiotics Typically Impacted |
|---|---|---|
| Reduced membrane permeability | Reduced production of OprD porin | Carbapenems (imipenem>meropenem) |
| Active antibiotic extrusion | Increased expression of MexAB-OprM efflux pump | Piperacillin, cefepime, meropenem, fluoroquinolones, tazobactam, avibactam, relebactam |
| Target site modification | Modification of PBP3 target | Ceftazidime, cefepime, aztreonam, cefiderocol, ceftolozane |
| | DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) | Fluoroquinolones |
| | Modifications in the outer membrane (e.g., PhoPQ, PmrAB) | Polymyxins |

| General Mechanisms | Examples | Antibiotics Typically Impacted |
|---|---|---|
| Reduced membrane permeability | Reduced production of OprD porin | Carbapenems (imipenem>meropenem) |
| Active antibiotic extrusion | Increased expression of MexAB-OprM efflux pump | Piperacillin, cefepime, meropenem, fluoroquinolones, tazobactam, avibactam, relebactam |
| Target site modification | Modification of PBP3 target | Ceftazidime, cefepime, aztreonam, cefiderocol, ceftolozane |
| | DNA gyrase (*gyrA*) and topoisomerase IV (*parC*) | Fluoroquinolones |
| | Modifications in the outer membrane (e.g., PhoPQ, PmrAB) | Polymyxins |
| Enzymatic modification | *Pseudomonas*-derived cephalosporinases (i.e., PDC) | Piperacillin, ceftazidime, aztreonam |
| | Carbapenemases (e.g., KPC, NDM, VIM) | Penicillins, cephalosporins, carbapenems, sometimes aztreonam |
| | Aminoglycoside-modifying enzymes (e.g., AAC, ANT, APH) | Aminoglycosides |

| 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 |
| Imipenem | 8 µg/mL | R |
| Meropenem | 8 µg/mL | R |
| Piperacillin-tazobactam | >64/4 µg/mL | R |
| Tobramycin | >8 µg/mL | R |

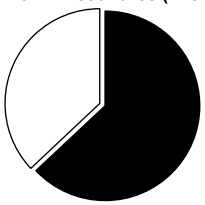
Difficult-to-treat resistance (**DTR**) defined as resistance to all traditional β-lactam and fluoroquinolone antibiotics


©2026 Infectious Disease Board Review, LLC

## *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

**Carbapenem-resistant *P. aeruginosa* isolates from 12 countries (n=542)**



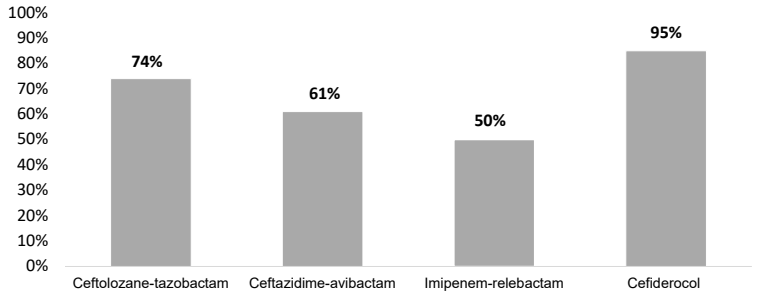
Kadri SS, et al. Clin Infect Dis 2018; 67: 1803-14. Gill CM, et al. Antimicrob Ag Chemother 2021;65:e0120421. Khalili Y, et al. Acta Microbiol Immunol Hung. 2019;66:529-540. Campana EH, et al. Braz J Infect Dis. 2017;21:57-62. Zeng ZR, et al. Diagn Microbiol Infect Dis. 2014;78:268-270.

## β-Lactam Landscape for DTR Infections

| Agents | 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 | | | | | | |
| Ceftazidime-avibactam | | | | | | |
| Meropenem-vaborbactam | | | | | | |
| Cefiderocol | | | | | | |
| Imipenem-cilastatin-relebactam | | | | | | |
| Sulbactam-durlobactam | | | | | | |
| Aztreonam-Avibactam | | | | | | |

## Contemporary Susceptibility Data for DTR *P. aeruginosa*

## Contemporary Susceptibility Data for DTR *P. aeruginosa*




Data from Antibacterial Resistance Leadership Group


©2026 Infectious Disease Board Review, LLC

## Cefiderocol



- Innate immune system minimizes available free iron in response to bacterial infections
  - Most iron in humans bound to hemoglobin, myoglobin, or the iron binding proteins
- Bacteria upregulate the production of their siderophores
  - Iron-chelating compounds that scavenge the human body for free iron
- Cefiderocol is a siderophore conjugated to a cephalosporin
- "Trojan Horse" approach to enter bacteria through iron transport channels
- Once across outer membrane it dissociates from iron molecule and binds to primarily to PBP3, disrupting cell wall synthesis

McCreary EK, et al. Antimicrob Agents Chemother. 2021;65:e0217120.

## Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

| Antibiotic | Empiric activity for index infection |
|---|---|
| Ceftolozane-tazobactam | |
| Ceftazidime-avibactam | |
| Cefiderocol | |
| Imipenem-cilastatin-relebactam | |

**Green** = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution

## Comparing Clinical Outcomes Across Agents

| Agent | ~Day 30 Survival | Study Type | Notes |
|---|---|---|---|
| Ceftolozane-tazobactam | ~80% | Observational data (n=427) | Performed **better** than polymyxin |
| Ceftazidime-avibactam | ~80% | Observational data (n=374) | Performed **better** than polymyxin |
| Imipenem-relebactam | 90% | Subgroup of clinical trial (n=16) | Performed **better** than polymyxin |
| Cefiderocol | 75% | Subgroup of clinical trials (n=38) | Performed **same** as polymyxin |

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;21:226-240. Shields RK, et al. Lancet Infect Dis. 2025;25:574-584. Lodise TP, J Antimicrob Chemother. 2024;79:2954-2964. Bassetti M, et al. Lancet Infect Dis. 2021;21(2):226-240. Paterson DL, et al. Lancet Infect Dis. 2026;26(2):148-159.

## Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

| Antibiotic | Empiric activity for index infection | Optimal clinical outcomes |
|---|---|---|
| Ceftolozane-tazobactam | | |
| Ceftazidime-avibactam | | |
| Cefiderocol | | |
| Imipenem-cilastatin-relebactam | | |

**Green** = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution


©2026 Infectious Disease Board Review, LLC

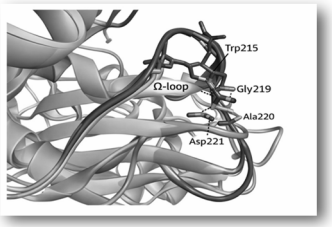
## Emergence of Resistance

- 28 consecutive patients with DTR *P. aeruginosa* isolates susceptible to ceftolozane-tazobactam and treated with ≥72 hours of ceftolozane-tazobactam
  - *P. aeruginosa* isolates before and after ceftolozane-tazobactam exposure evaluated by broth microdilution testing and sequencing (confirmation of genetic relatedness)
- **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.

## Acquired Resistance to Cephalosporin-Based Agents

- Resistant mutants commonly emerge because of amino acid changes in the catalytic center of *Pseudomonas*-derived cephalosporinases [**PDCs**]
- Enabling better accommodation of β-lactams with bulky R2 side chains
  - Ceftolozane, ceftazidime, cefepime, cefiderocol




Barnes M, et al. mBio. 2018 Dec 11;9(6):e02085-18.

## Acquired Resistance to Imipenem-Relebactam

- Typically result of a combination of the following:
  - **Loss of porins** (OprD reducing imipenem entry)
  - **PBP2 mutations** (target of imipenem)
  - **Increased production of efflux pumps** (MexAB-OprM and/or MexEF-OprN may efflux a portion of relebactam)
- Emergence of resistance to imipenem-relebactam while on therapy **~24%**

Gomis-Font MA, et al. J Antimicrob Chemother. 2020;75:2508-2515. Shields RK, et al. Clin Infect Dis. 2022;75(4):710-714.

## Acquired Resistance to Cefiderocol

- About **13%** of isolates had ≥4-fold increase in cefiderocol MICs in trials
- Mechanisms described:
  - Mutations in the iron transport system (e.g., *piu*, *pir*)
  - Increased expression of $bla_{VIM}$ or other carbapenemases due to increased copy numbers
  - Upregulation of PDCs or amino acid substitutions in catalytic center of PDCs
  - Upregulation of MexAB-OprM and other RND efflux systems
  - PBP3 mutations
  - OXA-2/OXA-10 ESBL mutations

Oliver A, et al. Clin Microbiol Infect. 2025:S1198-743X(25)00131-4. Karakonstantis S, et al. Antibiotics (Basel). 2022;11(6):723.


©2026 Infectious Disease Board Review, LLC

## Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

| Antibiotic | Empiric activity for index infection | Optimal clinical outcomes | Likelihood of sustained activity for subsequent infection |
|---|---|---|---|
| Ceftolozane-tazobactam | | | |
| Ceftazidime-avibactam | | | |
| Cefiderocol | | | |
| Imipenem-cilastatin-relebactam | | | |

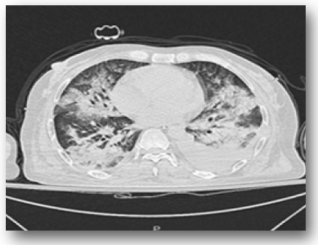
Using denominator of index isolates (and not subsequent *P. aeruginosa* isolates) to calculate emergence of resistance on therapy:

- **Ceftolozane-tazobactam: ~24%**
- **Ceftazidime-avibactam: ~24%**
- **Cefiderocol: ~10%**
- **Imipenem-relebactam: ~24%**

**Green** = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution

## Clinical Case: *P. aeruginosa*

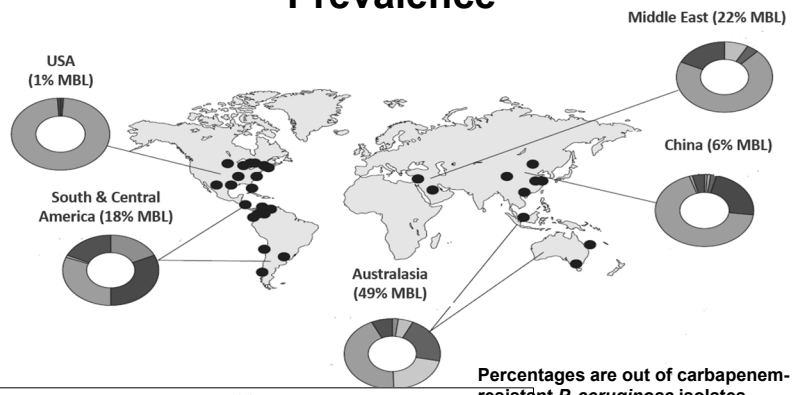
- 12-year-old male with acute myelogenous leukemia
  - Absolute neutrophil count = 0 cells/mL
- Developed acute onset fevers and respiratory distress
  - Multifocal pneumonia
- DTR *P. aeruginosa* recovered from bronchoalveolar lavage fluid



| 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 |

- Isolate contained a ***bla*$_{\text{VIM-2}}$** gene, a type of metallo-beta-lactamase **(MBL)** carbapenemase gene
- MBL-producing *P. aeruginosa* are **always resistant** to ceftolozane-tazobactam, ceftazidime-avibactam, & imipenem-relebactam

## MBL-Producing *P. aeruginosa* Prevalence




Reyes G, et al Lancet Microbe. 2023;4(3):e159-e170.

**Percentages are out of carbapenem-resistant *P. aeruginosa* isolates**


©2026 Infectious Disease Board Review, LLC

## Selecting Amongst Antibiotics with Activity Against DTR *P. aeruginosa*

| Antibiotic | Empiric activity for index infection | Optimal clinical outcomes | Likelihood of sustained activity for subsequent infection | Known VIM-producing carbapenemase |
|---|---|---|---|---|
| Ceftolozane-tazobactam | | | | |
| Ceftazidime-avibactam | | | | |
| Cefiderocol | | | | |
| Imipenem-cilastatin-relebactam | | | | |

**Green** = very favorable, **Yellow** = more likely to be favorable than not, **Purple** = proceed with caution/unlikely to be active

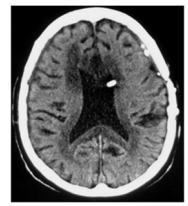
## Take Home Points

- Pros and cons to all β-lactams with activity against DTR *P. aeruginosa*
  - Select a susceptible agent (**ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam** > **cefiderocol**)
  - Retest subsequent DTR *P. aeruginosa* isolates
- VIM-producing *P. aeruginosa* isolates
  - Hint: Resistance to all available β-lactam-β-lactamase inhibitor combinations
  - **Cefiderocol** preferred

## Carbapenem-Resistant *Acinetobacter baumannii* (CRAB) Infections

## 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.


©2026 Infectious Disease Board Review, LLC

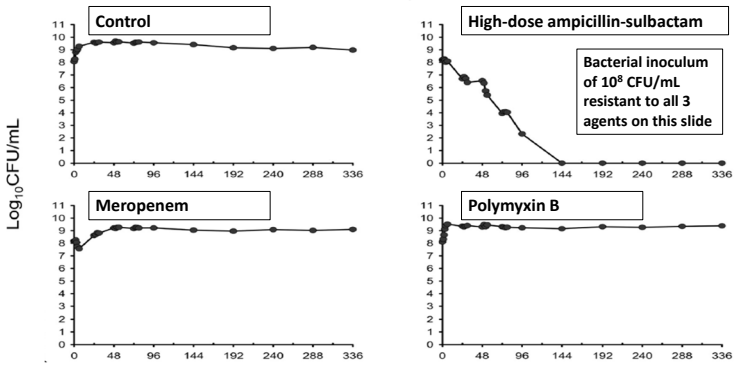
| Antibiotic | MIC | Interpretation |
|---|---|---|
| Amikacin | >32 µg/mL | R |
| Ampicillin-sulbactam | >16/8 µg/mL | R |
| Ceftazidime | >16 µg/mL | R |
| Ciprofloxacin | >2 µg/mL | R |
| Colistin | ≤1 µg/mL | I |
| Cefepime | >16 µg/mL | R |
| Gentamicin | >8 µg/mL | R |
| Meropenem | >8 µg/mL | R |
| Tobramycin | >8 µg/mL | R |
| Trimethoprim/sulfamethoxazole | >2/38 µg/mL | R |

# 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 Chemoth er. 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.

# Hollow Fiber Infection Model




Lenhard JR, et al. Antimicrob Ag Chemother. 2017;61:e01268-16.

**Red = mortality in patients with CRAB infections across clinical trials**

**Sirijatuphat, et al. (2014)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus fosfomycin (n=82)
- 28-day mortality (P=0.51):
  - **Colistin = 54%**
  - **Colistin + fosfomycin = 44%**

**Park, et al. (2019)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus rifampin for colistin-resistant CRAB infections (n=8)
- 30-day mortality (P=1.00):
  - **Colistin = 20%**
  - **Colistin + rifampin = 33%**

**Kaye, et al. (2023)**
- Multicenter, randomized, open-label trial
- Imipenem-cilastatin plus SUL-DUR vs. imipenem-cilastatin plus colistin (n=125)
- 28-day mortality (P=0.104)
  - **Imipenem + colistin = 32%**
  - **Imipenem + Sul-Dur = 19%**

**Khalili et al. (2018)**
- Single center, randomized open-label trial
- Colistin plus meropenem vs. ampicillin-sulbactam + meropenem (n=47)
- 28-day mortality (P=0.99):
  - **Colistin + meropenem = 42%**
  - **Amp-Sul + meropenem = 33%**

**Durante-Mangoni, et al. (2013)**
- Multicenter, randomized, open-label trial
- Colistin vs. colistin plus rifampin (n=209)
- 30-day mortality (P=0.95):
  - **Colistin = 43%**
  - **Colistin + rifampin = 43%**

**Mosaed, et al. (2018)**
- Single center, randomized, single-blind trial
- Colistin plus levofloxacin vs. Amp-Sul plus levofloxacin (n=33)
- 28-day mortality (P=0.04):
  - **Colistin + levofloxacin = 82%**
  - **Amp-Sul + levofloxacin = 42%**

**Bassetti, et al. (2020)**
- Multicenter, randomized, open-label trial
- Cefiderocol vs. alternative regimens (n=56)
- CRAB end of study mortality (P=0.038):
  - **Cefiderocol = 49%**
  - **Colistin-based = 18%**

**Pre-2013:** Numerous reports of synergistic combinations in vitro and encouraging observational studies

2013 2014 2018 2019 2020 2021 2022

**Paul, et al. (2018)**
- Multicenter, randomized, open-label trial with blinded outcome assessment (n=312)
- CRAB 28-day mortality (P=0.404)
  - **Colistin = 46%**
  - **Colistin + meropenem = 52%**

**Pourheidar, et al. (2019)**
- Single center, randomized, single-blind trial
- Colistin vs. ampicillin-sulbactam (both w/ inhaled colistin); (n=28)
- 28-day mortality (P=0.27):
  - **Colistin = 38%**
  - **Amp-Sul = 17%**

**Kaye, et al. (2022)**
- Multicenter, randomized, double-blind trial
- Colistin plus placebo vs. colistin plus meropenem (n=328)
- CRAB 28-day mortality (P=0.50)
  - **Colistin + placebo = 46%**
  - **Colistin + meropenem = 42%**

**Aydemir, et al. (2013)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus rifampin for CRAB infections (n=33)
- In-hospital mortality (P=0.66)
  - **Colistin = 73%**
  - **Colistin + rifampin = 62%**

**Makris, et al. (2018)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus high-dose ampicillin-sulbactam for CRAB infections (n=39)
- 28-day mortality (P=0.52):
  - **Colistin = 63%**
  - **Colistin + Amp-Sul = 50%**

Adapted from: Shields RK, et al. Clin Infect Dis. 2023, 76:S179-S193


©2026 Infectious Disease Board Review, LLC

**Red = mortality in patients with CRAB infections across clinical trials**

**Sirijatuphat, et al. (2014)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus fosfomycin (n=82)
- 28-day mortality (P=0.51):
  - **Colistin = 54%**
  - **Colistin + fosfomycin = 44%**

**Park, et al. (2019)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus rifampin for colistin-resistant CRAB infections (n=8)
- 30-day mortality (P=1.00):
  - **Colistin = 20%**
  - **Colistin + rifampin = 33%**

**Kaye, et al. (2023)**
- Multicenter, randomized, open-label trial
- Imipenem-cilastatin plus SUL-DUR vs. imipenem-cilastatin plus colistin (n=125)
- 28-day mortality (P=0.104)
  - **Imipenem + colistin = 32%**
  - **Imipenem + Sul-Dur = 19%**

**Khalili et al. (2018)**
- Single center, randomized open-label trial
- Colistin plus meropenem vs. ampicillin-sulbactam + meropenem (n=47)
- 28-day mortality (P=0.99):
  - **Colistin + meropenem = 42%**
  - **Amp-Sul + meropenem = 33%**

**Durante-Mangoni, et al. (2013)**
- Multicenter, randomized, open-label trial
- Colistin vs. colistin plus rifampin (n=209)
- 30-day mortality (P=0.95):
  - **Colistin = 43%**
  - **Colistin + rifampin = 43%**

**Mosaed, et al. (2018)**
- Single center, randomized, single-blind trial
- Colistin plus levofloxacin vs. Amp-Sul plus levofloxacin (n=33)
- 28-day mortality (P=0.04):
  - **Colistin + levofloxacin = 82%**
  - **Amp-Sul + levofloxacin = 42%**

**Bassetti, et al. (2020)**
- Multicenter, randomized, open-label trial
- Cefiderocol vs. alternative regimens (n=56)
- CRAB end of study mortality (P=0.038):
  - **Cefiderocol = 49%**
  - **Colistin-based = 18%**

**Pre-2013:** Numerous reports of synergistic combinations in vitro and encouraging observational studies

2013 | 2014 | 2018 | 2019 | 2020 | 2021 | 2022

**Paul, et al. (2018)**
- Multicenter, randomized, open-label trial with blinded outcome assessment (n=312)
- CRAB 28-day mortality (P=0.404)
  - **Colistin = 46%**
  - **Colistin + meropenem = 52%**

**Pourheidar, et al. (2019)**
- Single center, randomized, single-blind trial
- Colistin vs. ampicillin-sulbactam (both w/ inhaled colistin); (n=28)
- 28-day mortality (P=0.27):
  - **Colistin = 38%**
  - **Amp-Sul = 17%**

**Kaye, et al. (2022)**
- Multicenter, randomized, double-blind trial
- Colistin plus placebo vs. colistin plus meropenem (n=328)
- CRAB 28-day mortality (P=0.50)
  - **Colistin + placebo = 46%**
  - **Colistin + meropenem = 42%**

**Aydemir, et al. (2013)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus rifampin for CRAB infections (n=33)
- In-hospital mortality (P=0.66)
  - **Colistin = 73%**
  - **Colistin + rifampin = 62%**

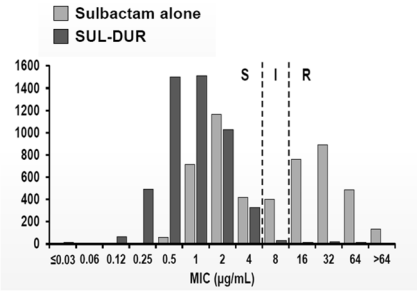
**Makris, et al. (2018)**
- Single center, randomized, open-label trial
- Colistin vs. colistin plus high-dose ampicillin-sulbactam for CRAB infections (n=39)
- 28-day mortality (P=0.52):
  - **Colistin = 63%**
  - **Colistin + Amp-Sul = 50%**

Adapted from: Shields RK, et al. Clin Infect Dis. 2023, 76:S179-S193

## Sulbactam-Durlobactam (Sul-Dur)

## 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.

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.


©2026 Infectious Disease Board Review, LLC

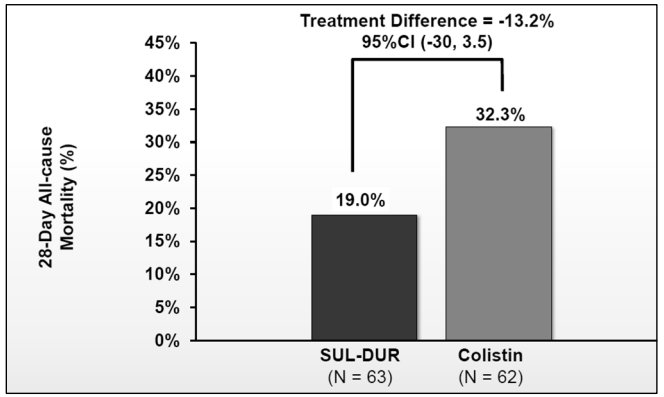
181 adults with *A. baumannii* pneumonia or bloodstream infections

**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.

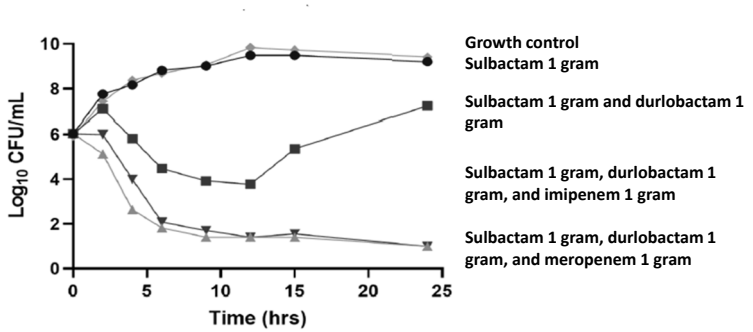



Kaye KS, et al. Lancet Infect Dis. 2023;23:1072-1084.

## Do We Need the Carbapenem?

- 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.




O'Donnell J, et al. Antimicrob Agents Chemother 2024;68:e0031223.


©2026 Infectious Disease Board Review, LLC

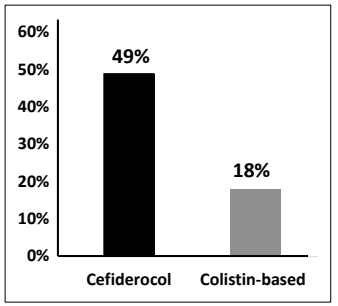
THE LANCET

## 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. 2021;21:226-240.

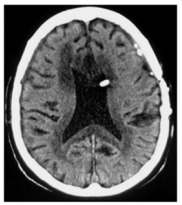
## End of Study Mortality for 54 Patients with CRAB infections




Bassetti M, et al. Lancet Infect Dis. Lancet Infect Dis. 2021;21:226-240.

## 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



- **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 |


©2026 Infectious Disease Board Review, LLC

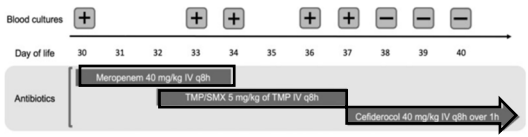
## Take-Home Points: CRAB

- Identification of CRAB in a clinical specimen does not always mean antibiotic therapy is indicated
- Sulbactam-based regimens remain the cornerstone of treatment
  - Preferred choice: **Sul-Dur** (with imipenem or meropenem)
  - Alternative choice: **High-dose Amp-Sul** (with an additional agent)
- Potential "additional agents" include **polymyxin B** or **minocycline** or **cefiderocol**

## *Stenotrophomonas maltophilia* Infections

## 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.

## 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

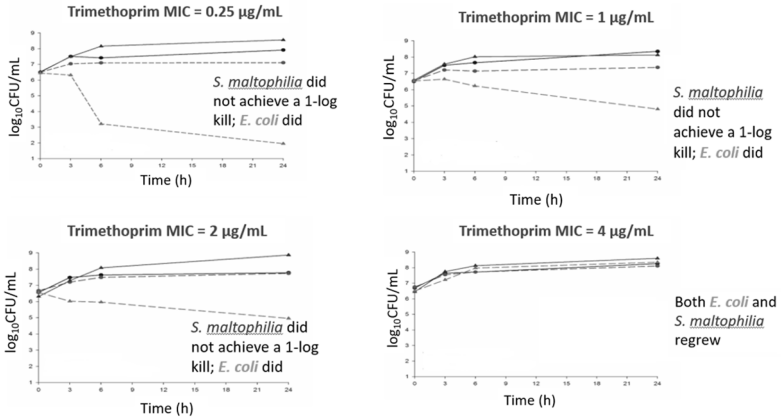
Mojica MF, et al. JAC Antimicrob Resist. 2022;4:dlac040. Brooke JS. Clin Microbiol Rev. 2012;25:2-41. Paez JI, et al. J Hosp Infect 2008;70:101-8. Karaba SM, et al. Antimicrob Agents Chemother 2021; 65:e0079321. Kim SH, et al. Eur J Clin Microbiol Infect Dis 2019; 38:285–95. Aitken SL, et al. Clin Infect Dis. 2021;72:1507-1513.


©2026 Infectious Disease Board Review, LLC

# TMP-SMX: Maybe Not as Reliable for *S. maltophilia* as We Once Believed?

- >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

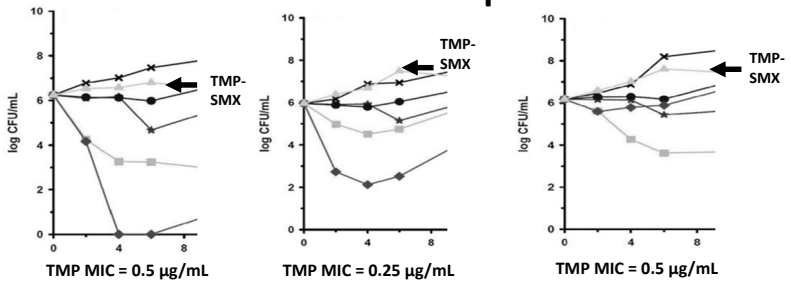
Fischer JJ. J Infect Dis 1973;128:Suppl:771-3. Dadashi M, et al. J Glob Antimicrob Resist 2023;34:253-67. Mendes ET, et al. Rev Inst Med Trop Sao Paulo 2020; 62: e96. Hu LF, et al. J Chemother 2018;30: 25–30.




**TMP-SMX human simulated dosages equivalent to 20 mg/kg/day**

Lasko MJ, et al. Antimicrob Agents Chemother. 2022; 66:e0216721.

# Additional Time-Kill Experiments



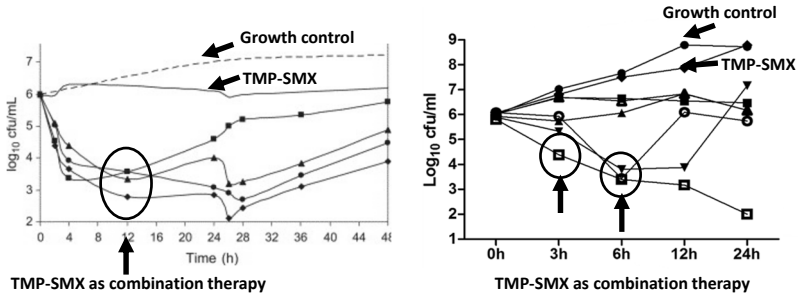

**TMP-SMX concentration was 4 times the TMP MIC for 3 TMP-susceptible isolates with no bactericidal activity observed.**

Biagi M, et al. Antimicrob Agents Chemother. 2020;64:e00559-20.

# Can Combination Therapy Improve the Activity of TMP-SMX?


©2026 Infectious Disease Board Review, LLC

## 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.

## Results from Monte Carlo Simulations

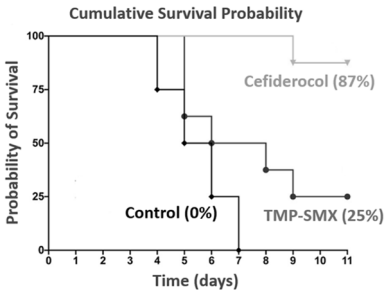
| TMP-SMX 10 mg/kg/day | *S. maltophilia* stasis | *E. coli* stasis |
|---|---|---|
| TMP MIC 0.5 µg/mL | **96%** | 100% |
| TMP MIC 1 µg/mL | 12% | 84% |
| TMP MIC 2 µg/mL | 0% | 2.5% |
| **TMP-SMX 15 mg/kg/day** | ***S. maltophilia* stasis** | ***E. coli* stasis** |
| TMP MIC 0.5 µg/mL | **100%** | 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.

## 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.

## Cefiderocol Clinical Data

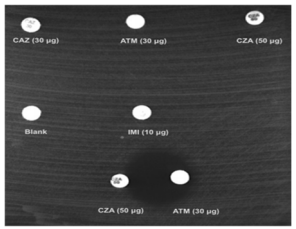
- Clinical trial comparing cefiderocol versus colistin-based regimens
  - All 5 patients with *S. maltophilia* infections randomized to cefiderocol arm
  - Treatment response for the 5 cases categorized as "indeterminant" with 4 of the 5 patients not surviving
- Several case reports suggest clinical 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.


©2026 Infectious Disease Board Review, LLC

## Aztreonam-Avibactam

- *S. maltophilia* is intrinsically resistant to most β-lactams because of two chromosomally encoded inducible β-lactamases
  - LI metallo-β-lactamase **(Aztreonam)**
  - 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.

## 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.

## 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.

## Minocycline

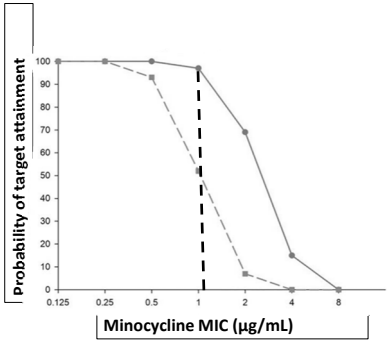
- Minocycline breakpoint against *S. maltophilia* is ≤1 µg/mL
- *S. maltophilia* susceptibility to minocycline ranges from ~35% to 90%
- *S. maltophilia* resistance to minocycline generally mediated by upregulation of several intrinsic multidrug-resistant efflux pumps

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


©2026 Infectious Disease Board Review, LLC

## 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**




Frantoni AJ, et al. J Antimicrob Chemother. 2022;77:1052-1060.

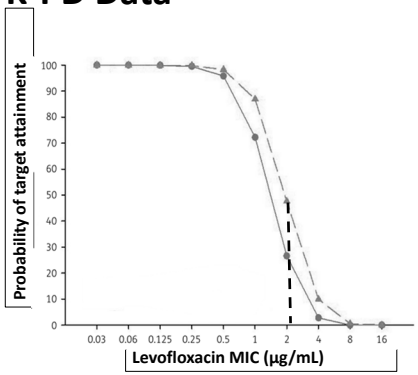
## Levofloxacin

- Levofloxacin breakpoint against *S. maltophilia* ≤2 µg/mL
- Susceptibility against approximately 80% of *S. maltophilia* isolates
- Resistance 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.

## 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.

## 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 AMR Guidance suggests **cefiderocol** as preferred therapy
- For non-severe infections combinations of **aztreonam-avibactam**, **TMP-SMX**, **minocycline**, or **levofloxacin** are suggested


©2026 Infectious Disease Board Review, LLC

Online Only Lectures

OL12

# Epididymitis, Orchitis, and Prostatitis

Barbara Trautner, MD

©2026 Infectious Disease Board Review, LLC

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Prostatitis, Epididymitis, and Orchitis

**Barbara Trautner, MD, PhD**
**Professor of Medicine**
**Washington University School of Medicine**
**St. Louis, Missouri**

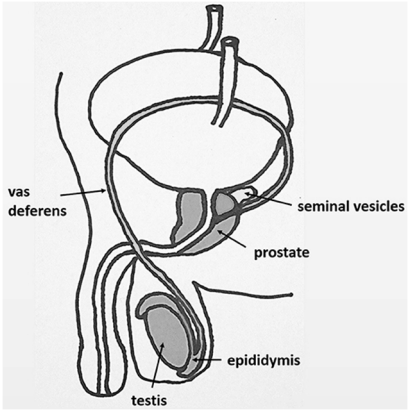
8/11/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Overview

- Epididymitis
- Prostatitis
  - Acute
  - Chronic
- Prostate biopsy
- Orchitis




## 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.


©2026 Infectious Disease Board Review, LLC

## Case #1 continued

Given his fevers on 2 days of ciprofloxacin, and the new awareness of right testicular pain and swelling, your next step is to:

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

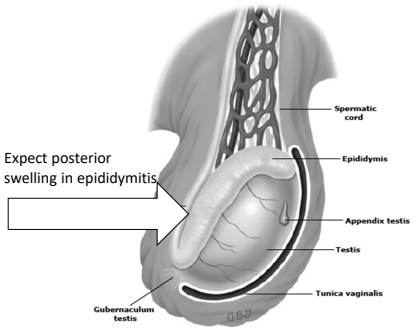


## Case #1 continued

Given his fevers on 2 days of ciprofloxacin, and the new awareness of right testicular pain and swelling, your next step is to:

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

**Normal testicular anatomy**




The testicle is vertical and its anterior portion is surrounded by the tunica vaginalis.

UpToDate®

Copyrights apply

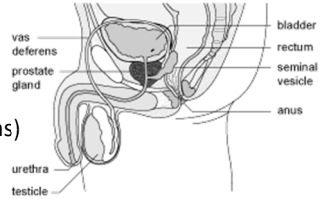
## Epididymitis: Clinical Presentation

- 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


©2026 Infectious Disease Board Review, LLC

## 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

## Etiologic agents of epididymitis

**>14 and < 35 years of age: typically sexually transmitted**

- *Neisseria gonorrheae*
- *Chlamydia trachomatis*
- *Mycoplasma genitalium*

**Chronic or atypical**

- *Mycobacterium tuberculosis*
- *Brucellosis*
- *Nocardia*
- *Blastomycosis*

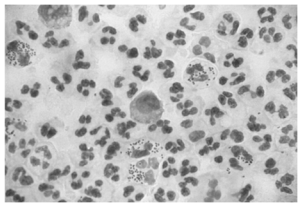
**> 35 years of age: enteric flora or spread from urine**

- *Escherichia coli*
- *Klebsiella*
- *Proteus*
- *Pseudomonas*
- Enterococci

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

## Workup of epididymitis

- Physical exam
  - Intact cremasteric reflex
  - Testes in normal location
  - No draining sinus
- Gram stain of urethral secretions
- Urinalysis and urine culture
- Nucleic acid amplification test (NAAT) of urine
  - *N. gonorrhoeae*
  - *C. trachomatis*
- Consider blood cultures
- If progression of soft tissue involvement
  - Consider necrotizing fasciitis
- Failure to improve within 48-72 hours
  - Scrotal ultrasound
- Call urology if concern for torsion



https://en.wikipedia.org/wiki/Neisseria_gonorrhoeae

Gram stain of urethral discharge

## Differentiating epididymitis from torsion

**Table 1. Selected Differential Diagnosis of Acute Scrotum**

| *Condition* | *Typical presentation* | *Examination findings* | *Ultrasound findings* |
|---|---|---|---|
| Epididymitis | Gradual onset of pain that occasionally radiates to the lower abdomen; symptoms of lower urinary tract infection | Localized epididymal tenderness that progresses to testicular swelling and tenderness; normal cremasteric reflex; pain relief with testicular elevation (Prehn sign) | Enlarged, thickened epididymis with increased blood flow on color Doppler |
| Orchitis | Abrupt onset of testicular pain | Testicular swelling and tenderness; normal cremasteric reflex | Testicular masses or swollen testicles with hypoechoic and hypervascular areas |
| Testicular torsion | Acute onset of pain, usually severe | High-riding transversely oriented testis; abnormal cremasteric reflex; pain with testicular elevation | Normal-appearing testis with decreased blood flow on color Doppler |

Trojian, American Family Physician, 2009


©2026 Infectious Disease Board Review, LLC

## Treatment of epididymitis

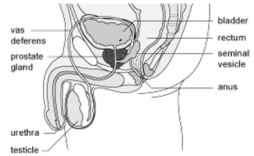



- If most likely STI (chlamydia or gonorrhea)
  - Ceftriaxone for *N. gonorrhea*
  - Doxycycline for chlamydia
- If risk for STI *and* enteric organisms
  - For example, insertive anal sex
  - Ceftriaxone for *N. gonorrhoeae*
  - Levofloxacin for chlamydia and enteric flora
- If most likely enteric organisms
  - For example, recent urologic procedure or catheterization or prior UTI
  - Levofloxacin, TMP/SMX
- For all: scrotal elevation and cold packs

UpToDate Acute Scrotal Pain in Adults
CDC https://www.cdc.gov/std/treatment-guidelines/epididymitis.htm
Trojian, American Family Physician, 2009

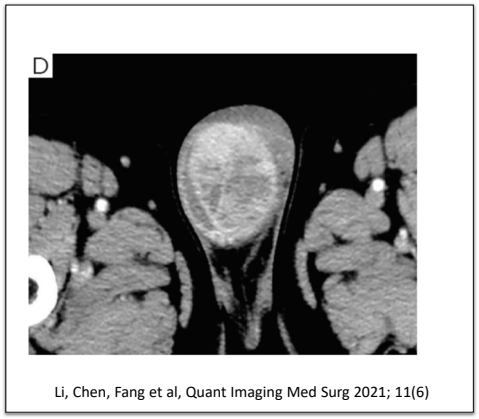
## Epididymitis: Management and Complications

- Medical management
  - Antibiotics
  - NSAIDS
  - Scrotal elevation and ice packs
- Complications
  - Testicular infarction
  - Scrotal abscess
  - Epididymo-orchitis




## Case #2

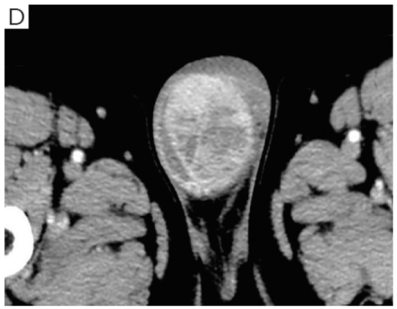
- 63 year-old man currently living homeless in Houston presented with a gradually enlarging, painful right testicle over the past 4 months
- Afebrile and he has thickened right scrotal skin but no fistula on exam
- WBC 15,000; negative HIV, AFP, RPR, and beta-HCG
- CT with contrast shows uneven enhancement of right testes and epididymis; the left epididymis was also enlarged with diffuse enhancement
- What test would you NOT do next?
  - A. TB spot
  - B. Urine culture for AFB
  - C. Testicular biopsy
  - D. Urine PCR for TB




Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)

## 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 fistulas 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-contraindicated in germ cell tumor, also can be insensitive/false negative**
  - D. Urine PCR for TB

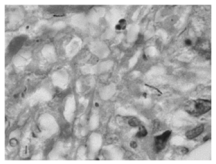



Li, Chen, Fang et al, Quant Imaging Med Surg 2021; 11(6)


©2026 Infectious Disease Board Review, LLC

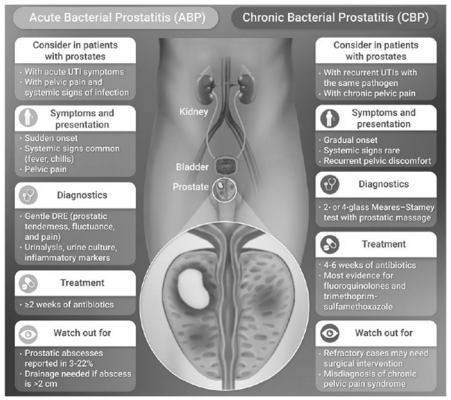
## Tuberculous epididymo-orchitis

- 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



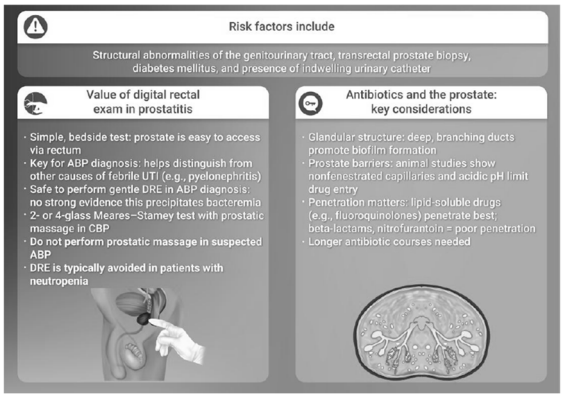
Yadav et al, Transl Androl Urol 2017
Liu et al, Surgical Infections 2021
Li et al, Quant Imaging Med Surg 2021

## Acute and Chronic Bacterial Prostatitis




Kulkarni et. al, State of the Art Review of Prostatitis, CID 2025

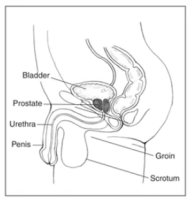
## Acute and Chronic Bacterial Prostatitis




Kulkarni et. al, State of the Art Review of Prostatitis, CID 2025

## 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


©2026 Infectious Disease Board Review, LLC

## Understanding the Prostatitis NIH Consensus Categories

| Condition | Bacteriuria | Localized to Prostate | Abnormal Rectal Exam | Systemic Illness |
|---|---|---|---|---|
| I Acute Bacterial Prostatitis | + | + | + | + |
| II Chronic Bacterial Prostatitis | + | + | +/-- | – |
| III Chronic Pelvic Pain Syndrome | – | – | – | – |
| IV Asymptomatic Inflammatory Prostatitis | – | – | +/-- | – |

McGowan, Chapter 110, in Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 9th edition

## Understanding the Prostatitis NIH Consensus Categories

| 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

## Case #3

A 69 year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He has chills and nausea in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

Management should include:

A. Nitrofurantoin
B. Urology consultation for catheterization
C. Culture of expressed prostatic secretions
D. PSA (prostate specific antigen) levels

## Case #3

A 69 year-old man presents with pain in the lower abdomen, rectum, and perineum for the past 48 hours. He also has chills in addition to urinary urgency, frequency, and dysuria. Gentle digital rectal examination finds a painful and swollen prostate. He has not been able to pass urine for the past 10 hours.

Management should include:

A. Nitrofurantoin-doesn't penetrate tissue or help with bacteremia
**B. Urology consultation for catheterization**—may need suprapubic, or transurethral placed with care
C. Culture of expressed prostatic secretions-do not massage the prostate firmly as this may cause bacteremia
D. PSA (prostate specific antigen) levels—will be elevated, non-specific


©2026 Infectious Disease Board Review, LLC

## Acute bacterial prostatitis: clinical presentation



- Acutely ill patient
- Prostatic tenderness is the distinguishing feature
- Fever, chills, irritative urinary symptoms
- Lower abdominal, rectal, or perineal pain
- Voiding difficulties
- Pathogenesis: from infection in the urinary tract, prostate biopsy, or hematogenous spread
- Risk factors: urinary catheters, urinary stasis, urinary instrumentation

UpToDate Acute Bacterial Prostatitis
Brede and Shoskes, Nat Rev Urol 2011

## Infectious prostatitis: Causative agents

**Acute** **> 60% caused by**

- *Escherichia coli*
- *Proteus*
- Other Enterobacterales
- *Pseudomonas*
- Staph, strep, enterococci
- *Salmonella typhi* (HIV)
- Burkholderia (traveler to SE Asia or N. Australia)
- STI: gonorrhea or chlamydia

**Chronic or immunocompromised**

- Same organisms as acute prostatitis
  - Enterococci more common
- Mycobacteria
- Fungal
  - Cryptococcus
  - Histoplasma
  - Aspergillus
  - Coccidioidomycosis
  - Candida
  - Blastomycosis
- Brucella

## Diagnostic workup of prostatitis

- Physical exam
  - Painful prostate
- Urinalysis and urine culture
- Consider blood cultures
- Failure to improve within 48-72 hours
  - Prostate ultrasound, computed tomography (CT) scan, MRI
- Call urology if unable to void

## Antibiotic treatment of acute bacterial prostatitis

- Most common pathogens are *E. coli* and other Enterobacterales
  - Microbiologic causes are very diverse
- Acute prostatitis, critically ill
  - Start broad—cephalosporins, pip/tazobactam, 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


©2026 Infectious Disease Board Review, LLC

## Case #4

A 72 year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation. What is the most common cause of a chronic form of this condition?

A. Herpes

B. Chlamydia

C. *E. coli*

D. Candida

## Case #4

A 72 year-old man presents with pain in the perineum, penile tip, and scrotum, which has been going on for the past three months. He had lower back pain a week ago, but the pain has since subsided. He has had two episodes of UTI with burning on urination in the past six months. On physical examination, his prostate is boggy and tender to palpation. What is the most common cause of a chronic form of this condition?

A. Herpes

B. Chlamydia

C. ***E. coli*** —most likely cause of chronic prostatitis especially given the history of recurrent urinary tract infection

D. Candida

## Chronic bacterial prostatitis

- Patients not acutely ill
- Recurrent UTI with same organism is common
- The four-glass Mears-Stamey test is cited often
- In practice urologists more often do the **two-glass test**
  - Urine samples pre/post prostatic massage
  - 10-fold higher bacterial counts post massage

Sharp et al, Am Fam Physician 2010

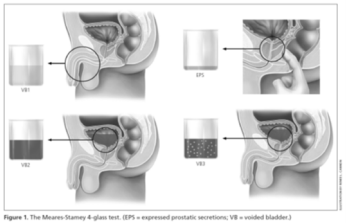


Figure 1. The Meares-Stamey 4-glass test. (EPS = expressed prostatic secretions; VB = voided bladder.)

## 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 **the best empiric choice**?

A. Amikacin

B. Fosfomycin

C. Ciprofloxacin

D. Trimethoprim-sulfamethoxazole


©2026 Infectious Disease Board Review, LLC

## 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 **an appropriate choice**?

**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

## Antibiotic prophylaxis for transrectal prostate biopsy

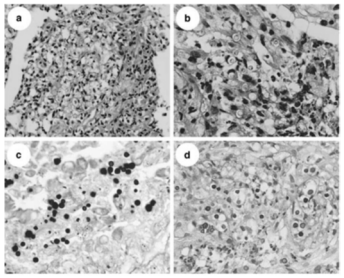
- Strongly recommended
- Pre-procedure antibiotics reduce the risk of bacteriuria, symptomatic UTI, bacteremia, fever, acute prostatitis, hospitalization
- No one best choice
- Options include fluoroquinolones, TMP/SMX, aztreonam, fosfomycin, and ceftriaxone plus gentamicin
- One dose, one hour to the 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

## 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. Biopsy revealed:

A. Candida
*B. E. coli*
C. Cryptococcus
D. Aspergillus
E. Nocardia

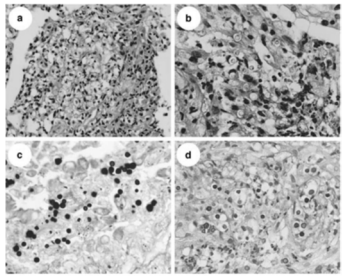


Wada et al, Prostate Cancer and Prostatic Dis 2008
Adams et al, Urology 1992
Wise and Shteynshlyuger, Curr Urology Rep 2006

## 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. Biopsy revealed:

A. Candida
*B. E. coli*
**C. Cryptococcus**
D. Aspergillus
E. Nocardia



Granulomas with round organisms that are clearly yeast on silver stain and have visible capsules


©2026 Infectious Disease Board Review, LLC

## 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. The likely causative agent is:

A. Mumps
B. Measles
C. *Escherichia coli*
D. *Neisseria gonorrhea*

## 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. The likely causative agent is:

**A. Mumps-parotid swelling and orchitis**
B. Measles
C. *Escherichia coli*
D. *Neisseria gonorrhea*



https://www.scientificamerican.com/article/a-mumps-outbreak-among-fully-vaccinated-people/

https://www.cdc.gov/mumps/about/photos.html

## Orchitis (isolated involvement of testes)

- Viral infections are common
  - Mumps
  - Coxsackie B
  - Lymphocytic choriomeningitis
- Bacterial
  - Contiguous spread from epididymis
  - Same organisms as epididymitis
    - *E. coli* and other enterics
    - Also same rare organisms (TB, fungal)




https://www.environmentandsociety.org/arcadia/mumps-post-secondary-environment-targeted-advertising-2007-2008-alberta-mumps-vaccination

## 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


©2026 Infectious Disease Board Review, LLC

## To Wrap Up:

- Epididymitis
  - Consider sexually transmitted infection versus *E. coli* and other enteric flora
- Prostatitis
  - Consider acute bacterial prostatitis in men with febrile UTI—detected by physical exam
  - Consider chronic bacterial prostatitis in men with recurrent or relapsing UTI
- Fungal, TB, and other indolent organisms (Brucella) can invade and infect the male genitourinary tract
- Isolated orchitis is rare in adults—consider viral etiology



## Is everything clear now?


- trautner@wustl.edu
- @bwtrautner





©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL13

# Bacterial and Viral Meningitis

**Allan Tunkel, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Viral and Bacterial Meningitis

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




## Disclosures of Financial Relationships with Relevant Commercial Interests

- None

## Question #1

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

## Question #1

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



©2026 Infectious Disease Board Review, LLC

# Question #1

5

**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

# Viral Meningitis
## Major Etiologies

6

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

# Cerebrospinal Fluid (CSF) Findings in Viral Meningitis

7

| 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 |

# Enteroviruses

8

- 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


©2026 Infectious Disease Board Review, LLC

## Enteroviruses

9

- Clinical clues
  - Time of year
  - Outbreak in community
  - Other recognizable enteroviral syndromes
- Specific etiologies
  - Scattered maculopapular rash: echovirus 9
  - Herpangina: coxsackievirus A
  - Pericarditis/pleuritis: coxsackievirus B
  - Rhombencephalitis: enterovirus 71

## Enteroviruses

10

- Symptoms and signs
  - Fever, headache, nuchal rigidity (>50%), photophobia
- Diagnosis
  - Neutrophils may predominate in CSF early (up to 48 hrs)
  - CSF virus isolation (sensitivity 65-75%)
  - Virus isolation from throat or rectum
  - PCR (sensitivity 86-100%; specificity 92-100%)
- Therapy
  - Supportive

## Mumps Virus

11

- Common in unimmunized populations
- Occurs in 10-30% of mumps patients overall
- Peak in children 5-9 years of age; males>females
- Can occur in patients without parotitis; 40-50% have no evidence of salivary gland enlargement
- Symptoms and signs usually follow onset of parotitis (if present) by ~5 days
- Diagnosis
  - Serology
  - CSF RT-PCR
  - CSF culture (sensitivity 30-50%)

## Herpes Simplex Virus

12

- 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



©2026 Infectious Disease Board Review, LLC

## Herpes Simplex Virus

13

- 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

## Lymphocytic Choriomeningitis Virus

14

- 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

## Question #2

15

- 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

## Question #2

16

- 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*


©2026 Infectious Disease Board Review, LLC

## Question #2

17

**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

## Question #2

18

**Which of the following diagnostic tests would most likely establish the pathogenesis of *E. coli* meningitis in this patient?**

A. MRI of the head and sinuses
B. Right upper quadrant ultrasound
C. **Serial stool examinations ***
D. Cisternography
E. Colonoscopy

## Epidemiologic Features of Pneumococcal Meningitis

19

- Most common etiologic agent in US (~58% of cases)
- Associated with other suppurative foci of infection
  - Pneumonia (25%)
  - Otitis media or mastoiditis (30%)
  - Sinusitis (10-15%)
  - Endocarditis (<5%)
  - Head trauma with CSF leak (10%)

## Epidemiologic Features of Meningococcal Meningitis

20

- Children and young adults (~7% of cases)
- 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


©2026 Infectious Disease Board Review, LLC

## Epidemiologic Features of Group B Streptococcal Meningitis

21

- Important etiologic agent in neonates (~21% of cases overall)
- Early-onset septicemia
- Late onset meningitis (>7 days after birth)
- Disease in adults less common:

| | |
|---|---|
| Diabetes mellitus | Parturient women |
| Cardiac, hepatic, renal disease | Malignancy |
| Collagen-vascular disorders | Alcoholism |
| HIV infection | Corticosteroid use |

## Epidemiologic Features of *Listeria* Meningitis

22

- Rare etiology in US (~3% of cases)
- 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 | TNF-alpha antagonists |

## Epidemiologic Features of *Haemophilus Influenzae* Meningitis

23

- Causes ~11% of cases in US
- 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 |

## Epidemiologic Features of Aerobic Gram-negative Bacillary Meningitis

24

- *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


©2026 Infectious Disease Board Review, LLC

## Other Bacterial Etiologies of Meningitis

25

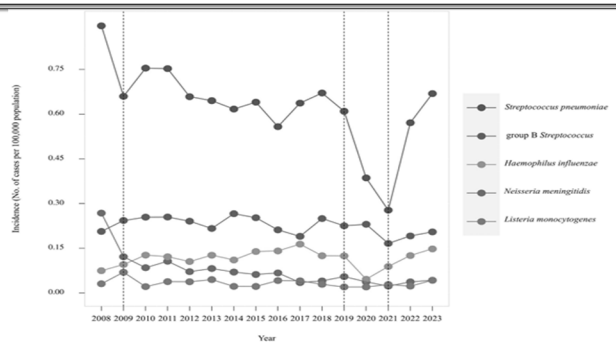
| Bacterial Etiology | Risk Factors |
|---|---|
| *Staphylococcus aureus* | Neurosurgery, trauma, diabetes mellitus, alcoholism, hemodialysis, injection drug use, malignancy |
| *Staphylococcus epidermidis* | CSF shunts and drains |
| Diphtheroids (e.g., *Cutibacterium acnes*) | CSF shunts and drains |
| Anaerobes | Contiguous foci in head and neck |
| *Streptococcus salivarius* | Spinal anesthesia, myelogram |
| *Streptococcus suis* | Vietnam, eating undercooked pig blood or pig intestine, pig exposure |

## Incidence of Bacterial Meningitis (United States)

26

| Organism | Incidence (cases per 100,000) | | |
|---|---|---|---|
| | 1986 | 1995 | 2006-2007 |
| *Haemophilus influenzae* | 2.9 | 0.2 | 0.08 |
| *Streptococcus pneumoniae* | 1.1 | 1.1 | 0.81 |
| *Neisseria meningitidis* | 0.9 | 0.6 | 0.19 |
| Group B streptococcus | 0.4 | 0.3 | 0.25 |
| *Listeria monocytogenes* | 0.2 | 0.2 | 0.05 |

## Incidence of Bacterial Meningitis (United States)




Prasad et al. Lancet Reg Health Am 2025;47:101120

## Cerebrospinal Fluid Findings in Bacterial Versus Viral Meningitis

28

| 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 |



©2026 Infectious Disease Board Review, LLC

## BioFire ® FilmArray ® Meningitis/Encephalitis Panel

29

| 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 | |

## Question #3

30

- 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$^{o}$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

## Question #3

31

**Which of the following empiric antimicrobial regimens should be initiated?**

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

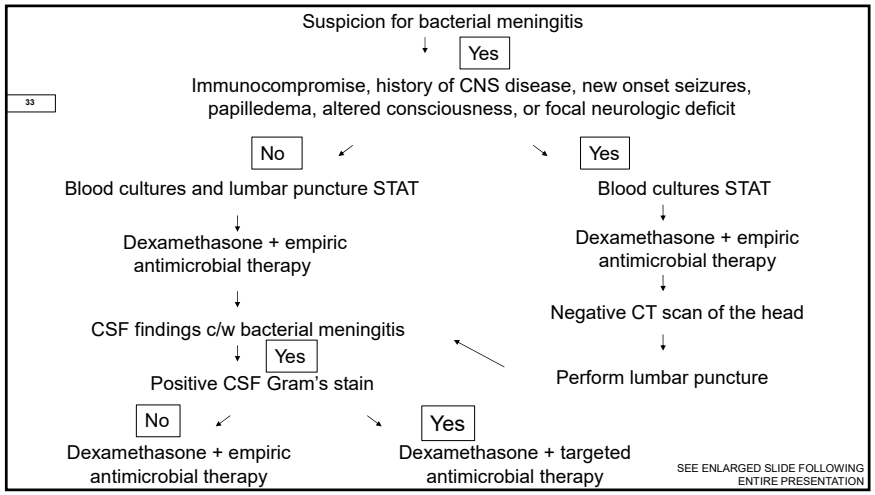
## Question #3

32

**Which of the following empiric antimicrobial regimens should be initiated?**

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


©2026 Infectious Disease Board Review, LLC




## Empiric Antimicrobial Therapy of Purulent Meningitis

34

| Age | Antimicrobial Therapy |
|---|---|
| <1 month | Ampicillin + gentamicin + either cefotaxime (if available) or cefepime |
| 1-23 months | Vancomycin + a third-generation cephalosporin[a] |
| 2-50 years | Vancomycin + a third-generation cephalosporin[a,b,c] |
| Older than 50 years | Vancomycin + ampicillin + a third-generation cephalosporin[a] |

[a]ceftriaxone or cefotaxime
[b]some experts would add rifampin if dexamethasone is also given
[c]add ampicillin if Listeria is suspected

## Empiric Antimicrobial Therapy of Purulent Meningitis

35

| 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

## Targeted Antimicrobial Therapy in Bacterial Meningitis

36

| 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


©2026 Infectious Disease Board Review, LLC

## Pneumococcal Resistance to Penicillin

37




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Pneumococcal Susceptibility to Penicillin

38

| | Minimal Inhibitory Concentration |
|---|---|
| Susceptible | ≤0.06 μg/mL |
| Resistant | ≥0.12 μg/mL |

## Antimicrobial Therapy in Bacterial Meningitis

39

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

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

## Antimicrobial Therapy in Bacterial Meningitis

40

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

[a]ceftriaxone or cefotaxime



©2026 Infectious Disease Board Review, LLC

## Antimicrobial Therapy in Bacterial Meningitis

41

| 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

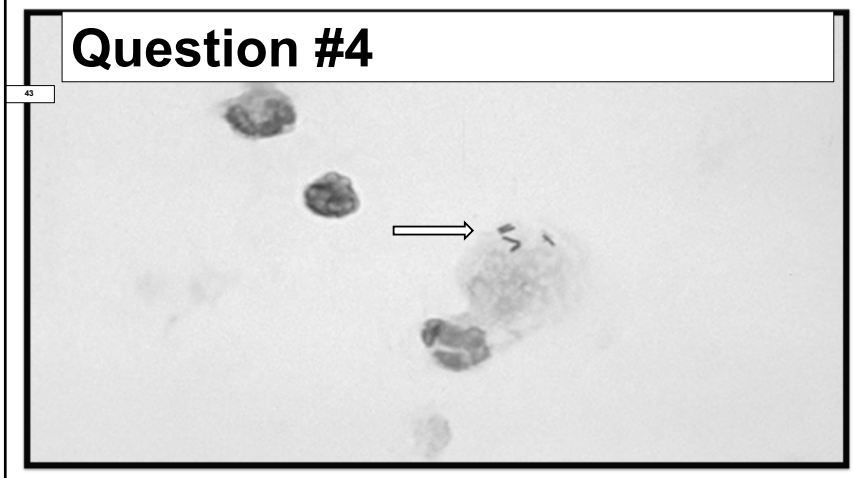
## Question #4

42

- 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

## Question #4

43



## Question #4

44

**Which of the following antimicrobial regimens should be initiated?**

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


©2026 Infectious Disease Board Review, LLC

# Question #4

45

## Which of the following antimicrobial regimens should be initiated?

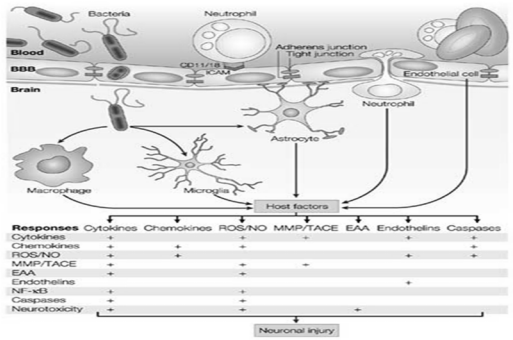
A. Vancomycin
B. **Trimethoprim-sulfamethoxazole ***
C. Chloramphenicol
D. Moxifloxacin
E. Daptomycin

# Case Fatality Rates in Bacterial Meningitis

| Microorganism | Overall Case Fatality Rates (2008-2023) |
|---|---|
| *Streptococcus pneumoniae* | 13.6% |
| *Neisseria meningitidis* | 9.7% |
| *Streptococcus agalactiae* | 10.2% |
| *Listeria monocytogenes* | 7.7% |
| *Haemophilus influenzae* | 4.3% |

# Adjunctive Dexamethasone in Bacterial Meningitis

47




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

# Adjunctive Dexamethasone in Bacterial Meningitis

48

- 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



©2026 Infectious Disease Board Review, LLC

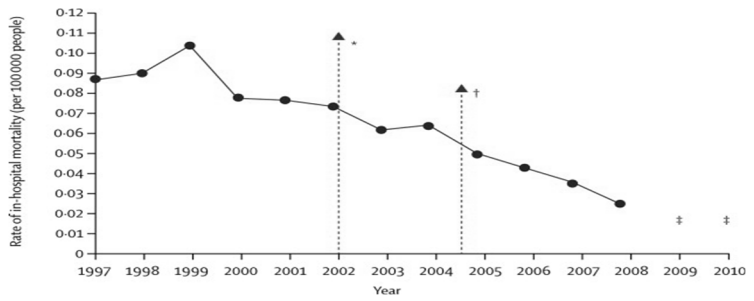
## Adjunctive Dexamethasone in Bacterial Meningitis

49

- 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

## In-Hospital Mortality for Pneumococcal Meningitis

50




Castelblanco et al. Lancet ID 2014;14:813

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

## Adjunctive Dexamethasone in Listeria Meningitis

51

- 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)






©2026 Infectious Disease Board Review, LLC

53

# QUESTIONS

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



©2026 Infectious Disease Board Review, LLC

## Online Only Lectures

---

# OL14

# Sinusitis and Otitis

**John Bennett, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.

# Otitis and Sinusitis

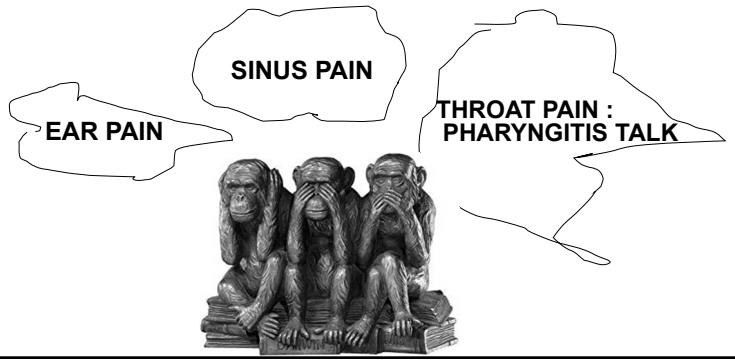
**John Bennett, M.D.**
**Bethesda, MD**

6/2/2026

## Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or “None”

## WHATS WRONG WITH THE THREE MONKEYS!



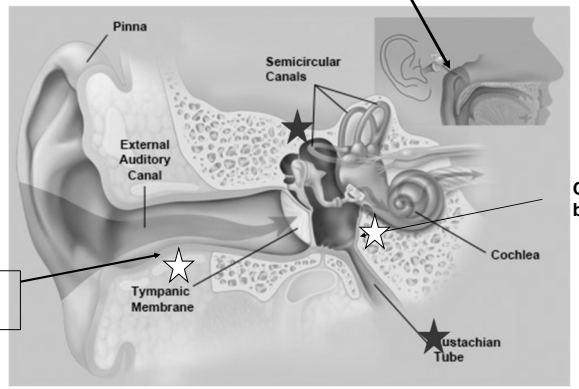

## OTITIS





©2026 Infectious Disease Board Review, LLC

## EAR ANATOMY




- **Acute otitis externa "swimmer's ear"**
- Cerumen, moisture. Maceration canal lining
- Cellulitis of external auditory canal.
- Canal red, edematous, full of debris and cerumen
- Tugging ear painful
- Staph aureus, epidermidis, C. acnes
- Rx. Gentle irrigation, cleansing. Wick if canal clogged.
- Burrow's ear drops. Cipro-hydrocortisone drops

## CASE: OTOMYCOSIS

- You are called to the ER because to see a 35 yr old man, otherwise healthy, who presented with "dull" hearing in his ear. On looking into the external auditory canal, the resident saw "black fuzz" blocking the canal, which he recognized was a fungus ball.
- Patient has no pain on pulling on his ear and no drainage but you see the black fuzz on the ear canal.
- What is the fungus and management of this condition?

## MANAGEMENT OF OTOMYCOSIS

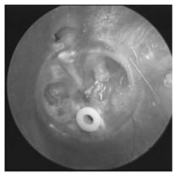
- Remove cerumen, debris and fungus by irrigation, cerumen spoon
- Otic drops (Burrow's) if canal lining inflamed. Antifungal not indicated.


©2026 Infectious Disease Board Review, LLC

## ACUTE OTITIS MEDIA

- Eustachian tube blockage (<4 yrs, adenoids, viral URI'S)
- Nasopharyngeal flora infects middle ear: pain, hearing loss
- Infection: TM red, bulging, immobile
- Pneumococcus, nontypable H. influenzae, Moraxella
- Rx 1st gen cephalosporin, etc

## CHRONIC SEROUS OTITIS



- Recurrent eustachian tube obstruction
- Painless hearing loss
- Middle ear becomes filled with fibrous tissue ("glue ear"), can lead to permanent healing loss
- Tympanometry, pneumatic otoscope
- "Pneumatic equalization" tube inserted into TM
- Adenoidectomy (rare)

## CASE

- 72yr old male, retired naval officer, presents in E.R. with increasing pain left ear of two day's duration. Given Augmentin + acetic acid/aluminum acetate ear drops in E.R. yesterday but pain worse. Laying head on pillow hurts, preventing sleep. Hearing "stopped up" on left. No chills, fever, cough or pain on chewing.
- PH DM 2. metformin
- PE T 38, P 92, BP 140/90. External auditory canal blocked by edema, cerumen. TM not visible. Tugging on left ear very painful. Mastoid not tender. No preauricular node.
- WBC 11.5 chems normal but glucose 180 mg/d.
- Differential diagnosis? Pathogen?

**77 yr old. severe ear pain, inflamed canal**

**The most likely pathogen is?**

A. Staphylococcus aureus
B. Aspergillus fumigatus
C. Streptococcus pyogenes
D. Pseudomonas aeruginosa
E. Rhizopus arrhizus



©2026 Infectious Disease Board Review, LLC

## ANSWER D. PSEUDOMONAS AERUGINOSA

## DIAGNOSIS:
**MALIGNANT (NECROTIZING) OTITIS EXTERNA**

## "INVASIVE" OTITIS EXTERNA
## AKA "MALIGNANT" OTITIS EXTERNA

- Diabetics and elderly
- Rapidly increasing pain in ear canal. Fever low grade or absent.
- Canal boggy, red. Pus. If TM visible, looks normal. Pinna painful if tugged.
- Hearing normal unless canal blocked by edema and debris
- Progression may extend anteriorly to temporomandibular joint or medially to 7$^{th}$ nerve
- Temporal bone osteo, sigmoid sinus thrombosis, brain abscess
- **Pseudomonas aeruginosa most common pathogen**
- Rx. Piperacillin-tazobactam or Ceftazidime or Cefepime 4-6 weeks

## CASE

A 70-year-old female in excellent health had 3-day history of stabbing pain and itching in her left ear.

On the second day of the pain, she developed pain in her left jaw, spreading to her left cheek. Chewing caused some pain in the left cheek, and she had some difficulty swallowing. Hearing was poor in her left ear.

On exam, she was afebrile, alert and oriented and had erythematous vesicles and moistness in the left external auditory canal plus some flattening of the nasolabial fold and lesser smile on the left. Sensoneural hearing loss in the left ear was present. The tympanic membrane could not be visualized because of pain on otoscopy.

## Healthy woman with ear pain, vesicles, Bell's palsy

**What diagnostic test on the ear exudate is most likely to yield the correct diagnosis?**

A. Routine bacterial culture
B. Fungal smear and culture
C. PCR for HSV
D. PCR for VZV
E. AFB smear and culture



©2026 Infectious Disease Board Review, LLC

## ANSWER: D. PCR FOR VZV
## DIAGNOSIS: Ramsay Hunt syndrome

- Herpes zoster of the geniculate ganglion of the 7th cranial nerve
- Pain in ear, vesicles in external auditory canal, Bell's palsy
- Can extend to 8th cranial nerve in internal auditory canal and cause deafness, vertigo or tinnitus (bad prognostic sign)
- Chorda tympani branch: taste distortion, numb or burning
- Early IV acyclovir to decrease permanent nerve damage

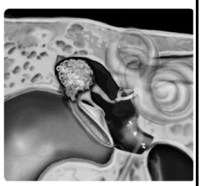
## CASE

- ENT consults ID for treatment of chronic otitis media
- 56 yr female, otherwise healthy, treated with multiple courses of antibiotics for chronically draining ear. tm has marginal perforation. CT shows fluid in mastoids. swab from external canal has MRSA and mixed gram negative flora.
- No drug allergies. Prior regimens:
  - Amoxicillin, cipro, augmentin, moxifloxacin
- Drainage less then relapses
- Management?



## CHRONIC OTITIS MEDIA/MASTOIDITIS

- Failed treatment of acute otitis media, presents as chronic drainage from ear and decreased hearing. tm perforated
- Cholesteatoma can form from perforation or "retraction pocket" in TM. Erodes bone/ossicles
- Rx mastoidectomy + removing cholesteatoma
- Rx prolonged antibiotics
- NTM, Aspergillus, TB rare causes



## CASE

- A 22-year-old, male: two years of painless purulent drainage and progressive hearing loss in his right ear which is now profound. Treated numerous times with various antibacterial drugs for Staph aureus and Pseudomonas without improvement. He was born in Korea but has lived in San Francisco since age 11.
- Afebrile, no night sweats or weight loss. No remarkable physical findings or laboratory findings except for extensive granulation tissue and drainage in his right external auditory canal and a large tympanic membrane perforation. HIV testing is negative. CT Imaging of his chest is normal. CT scan: partial opacification of the right mastoid air cells.



©2026 Infectious Disease Board Review, LLC

**Korean-borne man with 2 yrs painless ear drainage**

**What is the most likely cause of this chronic otitis?**

A. Granulomatosis with polyangiitis (Wegeners)
B. Syphilis
C. Polychondritis
D. Tuberculosis
E. Actinomycosis

## ANSWER: D. TUBERCULOSIS

- **TB Otitis**
  - Usually unilateral, relatively painless, progresses over months
  - TM perforated. Drainage in canal. Mastoid fluid.
  - May have preauricular adenopathy, ipsilateral facial palsy
  - May extend to contiguous bone, brain
  - Chest CT normal in half
  - Dx. AFB smear, culture, PCR of drainage or biopsy
- **Granulomatosis with polyangiitis** (Wegener's granulomatosis). Similar picture but also lung, paranasal sinus or kidney disease

## CASE

- 56 yr old woman with insulin dependent diabetes presents with 1 week of worsening right sided headache and a new onset horizontal diplopia, worse when looking to the right. For several weeks she has had chronic purulent drainage from her right ear.

- On exam she is afebrile. Otoscopic exam reveals purulent otorrhea and a perforated tympanic membrane on the right. Neurologic exam show inability to abduct the right eye. Which of the following explains the mechanism of her neurologic findings.

## Woman with draining ear, headache and CN 6 palsy

### Mechanism of neurologic findings?

A. Reactivation of varicella-zoster virus in the geniculate ganglion
B. Extension of middle ear infection to the petrous apex, involving the abducens nerve
C. Invasive fungal infection of the external auditory canal
D. Granulomatous inflammation of small and medium sized arteries
E. Cavernous sinus thrombosis due to hematogenous spread



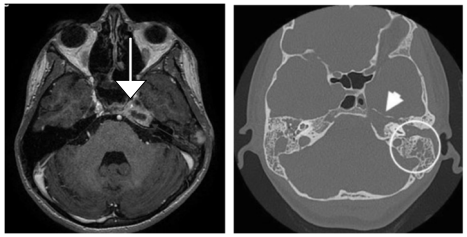
©2026 Infectious Disease Board Review, LLC

**ANSWER: B. Extension of middle ear infection to the petrous apex, involving the abducens nerve**
**DIAGNOSIS: Gradenigo syndrome, petrous apicitis**

- Subacute/chronic mastoiditis, (mastoid in circle below in CT)
- Infection extends medially to petrous pyramid (white arrow in CT)
- Abscess damages CN 6 (yellow arrow in MRI).

Rx IV antibiotics

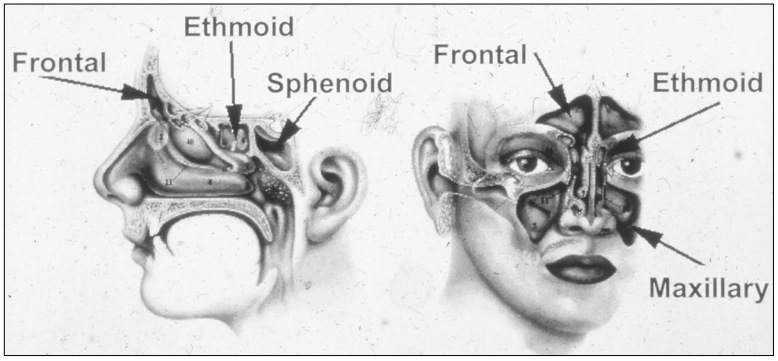
Later: mastoid surgery



## SINUSITIS



## LOCATION OF THE SINUSES




## CASE

- In January in Chicago, a 30-year-old woman in excellent health has had purulent nasal drainage, fevers to 38.5°C, sore throat, and chills for the past 12 days.
- She has been able to work and exercise on the treadmill as usual, but is easily fatigued. She saw her primary care physician after 5 days of symptoms, who was insistent that she did not need antibiotics because her symptoms were of short duration and likely would resolve without antibiotics.
- She comes to you as an ID physician for another opinion, a week after seeing her primary care physician.
- She has a temperature of 38.3°C with intermittent chills, moderate pain over her sinuses, and purulent-looking nasal discharge. Her WBC is normal. She has no drug allergies.



©2026 Infectious Disease Board Review, LLC

## Healthy woman with acute sinusitis 12 days

**What would be the best choice for management?**

A. Nasal decongestant and nasal irrigations with saline twice daily for 3-5 days but no antibiotics unless her clinical syndrome worsens
B. Clindamycin
C. Cephalexin
D. Amoxicillin-clavulanate
E. Ciprofloxacin

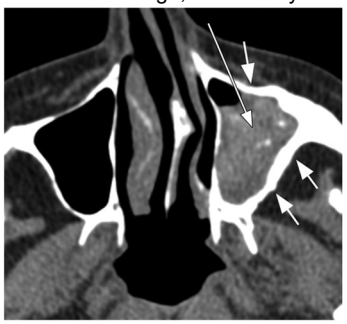
## ANSWER: D. AMOXICILLIN-CLAVULANATE

Fever and 12 days suggests bacterial, despite normal WBC

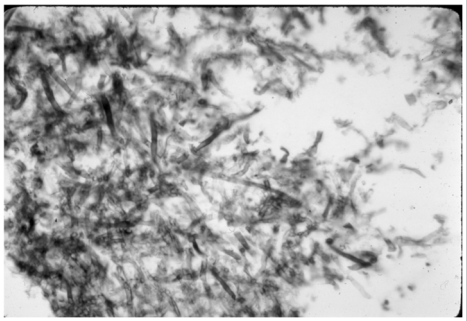
Amoxicillin-clavulanate offers best coverage for Pneumococcus and beta-lactamase positive nontypable

Hemophilus influenzae and Moraxella.

**FUNGUS BALL OF THE SINUS**
Aspergillus or other molds grow in mucus of chronically obstructed sinus. Calcified clumps may appear.
Rx: curettage, antrostomy



**Surgical specimens of fungus balls in the sinus have hyphae embedded in a matrix of debris**



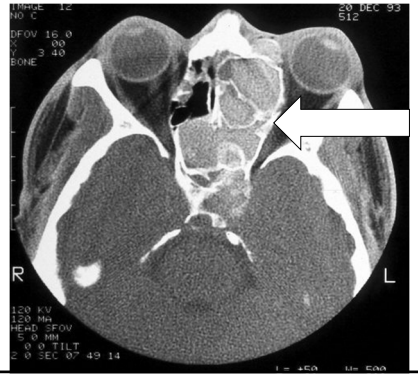
## CASE

- An otolaryngologist referred an 18-year-old male from Baltimore following sinus surgery because hyphae were seen in the histopathology of sinus tissue.
- The patient had sought help from his internist for months of gradually increasing painless protrusion of his left eye. He had been otherwise well except for a history of hay fever and allergic rhinitis, for which he sometimes used nasal sprays with a decongestant or corticosteroid. On exam he was afebrile and had proptosis of his left eye. Visual acuity was normal. The internist ordered a sinus CT. The ethmoid sinus was full of tissue, the walls bulged info the orbit, causing the proptosis.



©2026 Infectious Disease Board Review, LLC

## CT: EXPANSILE MASS FILLING LEFT ETHMOID SINUS AND PUSHING ORBIT OUTWARDS




Patient referred to ENT, taken to surgery, ethmoid curetted, uncomplicated postop course until path reports showed hyphae. ID consulted.

- SURGERY: sticky dark mucus was curetted from the sinuses. Mucosa hyperplastic.
- PATHOLOLGY: occasional hyphae in mucus but not in mucosal lining, eosinophils, and occasional Charcot-Leyden crystals
- CULTURE: brown mold that was sent to a reference laboratory for identification.

## Allergic boy with painless proptosis who had this CT scan of ethmoidal sinus

**Which of the following offers the most appropriate curative therapy for this condition?**

A. Surgical removal of all sinus contents
B. Itraconazole
C. Posaconazole
D. Amphotericin B IV
E. Nasal wash with amphotericin B



## ANSWER: A. REMOVAL OF ALL SINUS CONTENTS

## DIAGNOSIS: ALLERGIC FUNGAL SINUSITIS

- Healthy patient with nasal obstruction, painless proptosis
- Follow surgery with endoscopy and CT to look for relapse (common)
- Antifungals: no role
- Nasal corticosteroid spray or dupilumab to prevent recurrence?

- Review: (Laryngoscope 2001; 110:799-813)
- Age: 3-74 yr (mean 31 yr) m:f=1:1
- Prior hx nasal polyps (95%), allergic rhinitis (84%), +/-asthma (41%)
- Eosinophilia (70%), high IgE (83%)



©2026 Infectious Disease Board Review, LLC

## ACUTE FUNGAL SINUSITIS

- Covered in mycoses lecture
- Aspergillosis:
  - Prolonged neutropenia, transplant. Immunosuppressed
- Mucormycosis
  - Poorly controlled diabetes, neutropenia, immunosuppression

## CASE

- A 23-year-old previously healthy female presents with a two-day history of a progressively red and painful right eye and low-grade fever. Her vision is slightly blurred. She has no history of local trauma or recent surgery and is aware of no other recent illness. She works in retail in Chicago. She is sexually active with a new male partner.
- On physical examination she is febrile to 38.3°C, and has a right ophthalmoplegia involving cranial nerves III, IV, and VI. The right eyelid is swollen and erythematous. Her right pupil reacts sluggishly to light. There is marked chemosis, periocular edema and proptosis. The retina appears normal.
- His laboratory examination is normal except for WBC = 17000/$mm^3$ (90% neutrophils). HIV test is negative.

**2 days painful red swollen eye now blind, proptotic**

**The most likely diagnosis is which of the following?**

A. Staphylococcal blepharitis
B. Gonococcal conjunctivitis
C. Bacterial orbital cellulitis
D. Bacterial preseptal cellulitis
E. Behcet's disease



## ANSWER: C. BACTERIAL ORBITAL CELLULITIS

- **Preseptal** infections: eyelids, conjunctiva, skin around eye
- **Postseptal** infections: intraorbital
- Orbital cellulitis:
  - usually originates from ethmoid sinus
  - fever, leukocytosis, vision loss
  - iv antibiotics, sinus surgery
- Cavernous sinus thrombophlebitis: similar presentation
  - vision loss late, high fever
  - source is sinus or face



©2026 Infectious Disease Board Review, LLC

## Back to the monkeys

Too much information!

Too many slides!

Time to stop talking!





©2026 Infectious Disease Board Review, LLC

**Online Only Lectures**

---

**OL15**

# Kitchen Sink: Syndromes Not Covered Elsewhere: Bonus Cases

**Stacey Rose, MD**

**©2026 Infectious Disease Board Review, LLC**

COPYRIGHT NOTICE: The Copyright Act (Title 17 of U.S. Code) governs the rights attributed to owners of copyrighted work. Under certain circumstances, educational institutions may provide copies of copyrighted works to continuing education participants. The copies may not be copied or used for any other purpose besides private study, scholarship, or research. Participants should not provide electronic or print copies of any materials provided by the university to unauthorized users. If a participant fails to comply with these restrictions, the participant may be held liable for copyright infringement. No further transmission or electronic distribution is permitted.




# Kitchen Sink: Syndromes Not Covered Elsewhere (online content)

**Stacey R. Rose, MD, FACP, FIDSA**
**Associate Professor of Medicine, Infectious Diseases**
**Director, Center for Professionalism**
**Baylor College of Medicine**

8/11/2026




## Disclosures of Financial Relationships with Relevant Commercial Interests

- List of disclosures or “None”




## Session Plan

- Case-based discussions of topics not extensively covered in other sessions
- Highlight points likely to be assessed on ID Boards (rather than comprehensive overview)



## Question #1



- 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 *Bordetella pertussis*.
- She works as a nurse in a pediatric intensive care unit and would like guidance for when she can return to work.



**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**
*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

# Question #1



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

5

# Question #1



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

6

## 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.

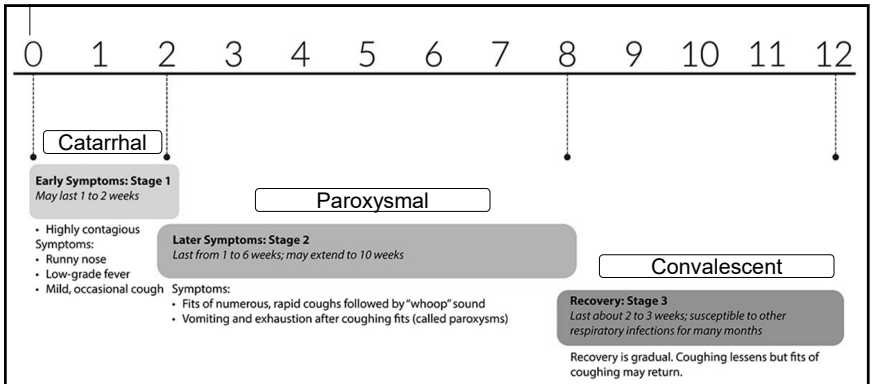
April 22, 2025

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/ 7




***Pertussis: Clinical Stages***

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/pertussis/index.html 8

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

## 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



## 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.



## Pertussis: Recommendations for Health Care Workers (HCW)



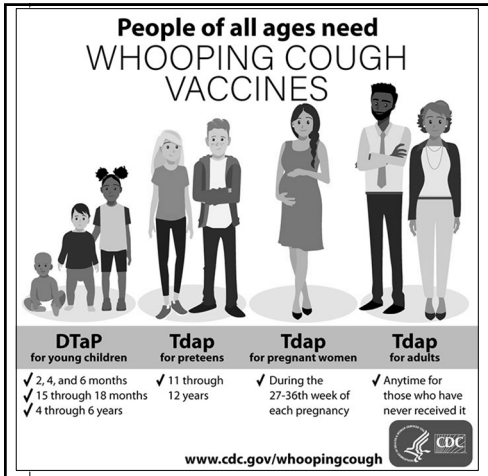
**Symptomatic infection**: exclude from work for 21 days from onset of cough OR until 5 days after the start of effective antimicrobial therapy



**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






## Pertussis Vaccination

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/pertussis/vaccines/index.html



**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC



- **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

13

## Question #2



- 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.

14

## Question #2

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

15

## Question #2

You note that antibiotic therapy for uncomplicated appendicitis has become accepted practice by some physicians and offer to counsel him regarding risks and benefits.

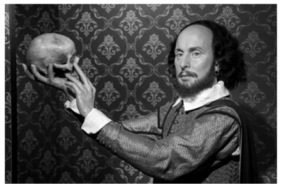
**Which of the following is a recognized disadvantage of this approach, when compared to immediate surgery?**

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**

16


©2026 Infectious Disease Board Review, LLC

## 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

17



## 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

18



- 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 necessary

## Appendicitis

Take Home Points

19

## Question #3

- 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.

20

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**
*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

# Question #3

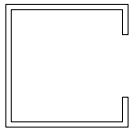


Indian J Dermatol. 2010;55(1):79-85.

- 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.



# Question #3

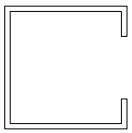


**Which of the following tests is most likely to yield the diagnosis?**

*A.* *Dengue* real-time PCR
B. Blood culture
*C.* *Lyme* enzyme immunoassay (EIA)
*D.* *Malaria* rapid diagnostic test (RDT)



# Question #3



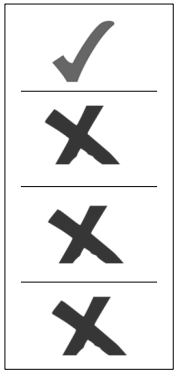
**Which of the following tests is most likely to yield the diagnosis?**

***A.* *Dengue* real-time PCR**
B. Blood culture
*C.* *Lyme* enzyme immunoassay (EIA)
*D.* *Malaria* rapid diagnostic test (RDT)



# Question #3 - Explained

Fever, headache, body pain, rash and low platelets in a returning traveler



**Dengue** – characteristic symptoms and epidemiology; PCR or NS1 antigen test recommended within first 7 days

**Blood culture** – presumably looking for Typhoid fever, but rash is not characteristic and no gastrointestinal symptoms

**Lyme** – wrong epidemiology (no known exposure to ticks) and rash not typical for Lyme; low platelets does not fit

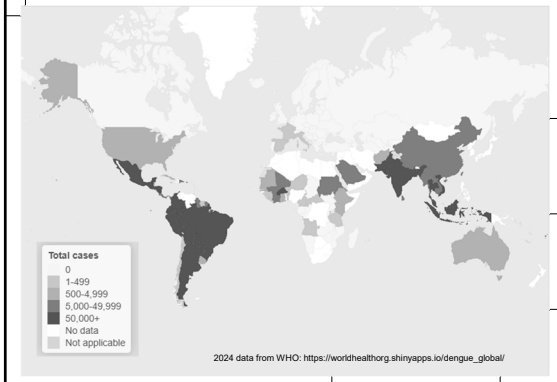
**Malaria** – RDT would be diagnostic, but no anemia and rash not typical with malaria; also was taking prophylaxis





©2026 Infectious Disease Board Review, LLC

## Dengue is Common Worldwide…and Rising



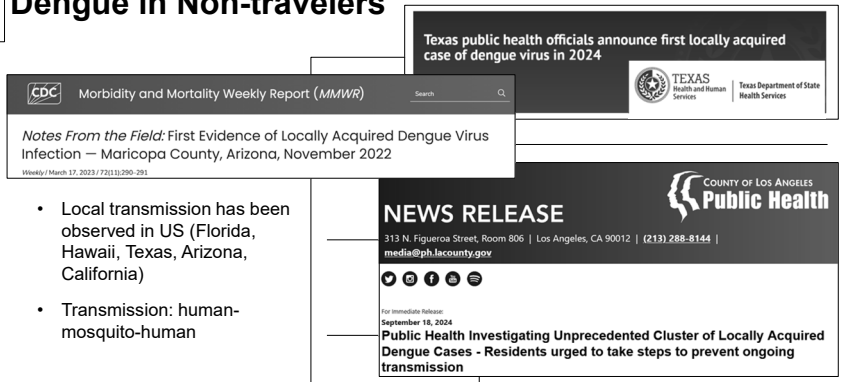

- 100-400 million infections each year worldwide
- Tropical and subtropical climates
- Urban and semi-urban areas

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/dengue/outbreaks/2024/index.html

25

## Dengue in Non-travelers

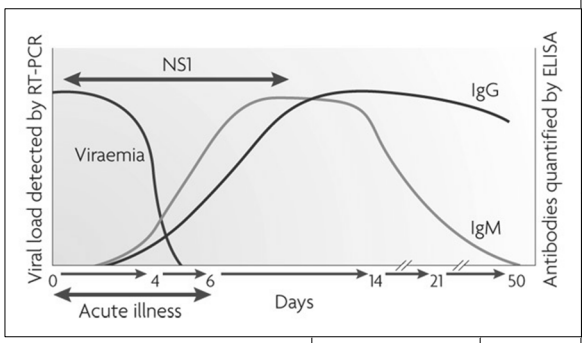



- Local transmission has been observed in US (Florida, Hawaii, Texas, Arizona, California)
- Transmission: human-mosquito-human

https://www.cdc.gov/dengue/outbreaks/2024/index.html

26

## 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

27

## 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

28

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

# Mosquito-borne Illnesses in a Returning Traveler



Aedes aegypti mosquito, image from https://www.cdc.gov/mosquitoes/about/life-cycle-of-aedes-mosquitoes.html

**For the boards, know:**

- Typical epidemiology
- Clinical presentation
- Vector
- Diagnostic approach

29

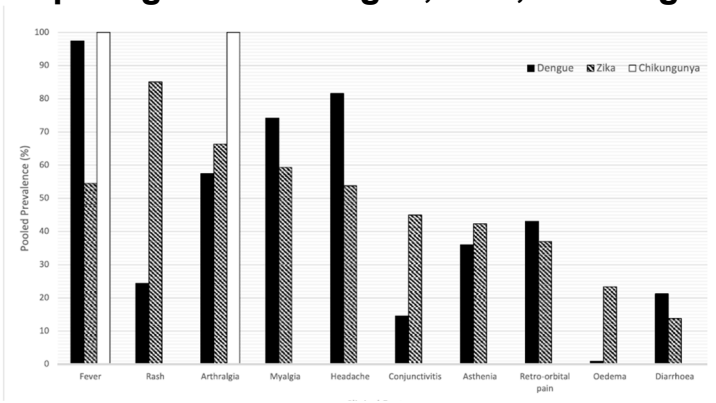
# Key Features of Mosquito-borne Illnesses

| | Epidemiology | Vector | Clinical Features |
|---|---|---|---|
| Chikungunya | Africa, the Americas, Asia, Europe, islands in Indian and Pacific Oceans; prominent outbreak Caribbean 2013 | ***Aedes** aegypti* (*A. albopictus* in Europe) | Fever and **joint pain**; rash less common. Symptoms may last months. |
| Dengue | Worldwide in tropics / subtropics<br><br>4 serotypes; infection with a 2nd serotype → severe illness | ***Aedes** aegypti* (or *A. albopictus*) | Fever, **headache**, **rash**, **muscle and joint pain**<br><br>Severe: **shock** / **hemorrhage** |
| Zika | Prominent in Americas ~2017, then more widespread (Caribbean, Africa, India) | ***Aedes** aegypti*<br><br>**Also sexual transmission; maternal-fetal infection** | Often asx; fever; **rash** (starts on face); **conjunctivitis**<br><br>Fetal anomalies (**microcephaly, blindness**) |

CDC; PPID 9th edition

30

# 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.

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

31




A Comprehensive Review of the Neglected and Emerging Oropouche Virus. Viruses. 2025

# (Not So) New and Notable: Oropouche 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

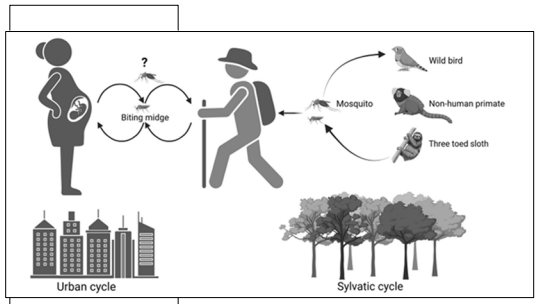
32



©2026 Infectious Disease Board Review, LLC

## Oropouche Virus

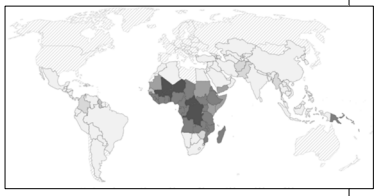
- **Clinical features**: **fever**, headache, myalgia, arthralgia
  - Rash *not* common
  - Rarely, encephalitis
  - **Fetal anomalies** (microcephaly, fetal demise)
- **Diagnosis** – PCR within first 5 days




SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

A Comprehensive Review of the Neglected and Emerging Oropouche Virus. Viruses. 2025

33



https://ourworldindata.org/malaria

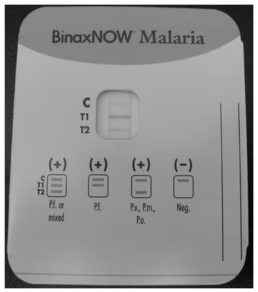
## Malaria

- **Epidemiology**: worldwide, tropics and subtropics
- **Vector**: *Anopheles* mosquito
- **Symptoms**: Fever, headache, N/V, diarrhea; severe: anemia, jaundice, splenomegaly, neurologic
- *Species-specific* features

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

https://www.cdc.gov/malaria/hcp/diagnosis-testing/malaria-diagnostic-tests.html

34




## 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

35

### An unusual surge in cases

In 2023, CDC received reports of 10 cases of locally acquired malaria in four states, with nine cases caused by *P. vivax* among people with no travel history in Florida, Texas, and Arkansas.

| | |
|---|---|
| **Florida** | 7 *P. vivax* cases |
| **Texas** | 1 *P. vivax* case |
| **Maryland** | 1 *P. falciparum* case |
| **Arkansas** | 1 *P. vivax* case |

https://www.cdc.gov/advanced-molecular-detection/php/success-stories/malaria-parasite-2023.html

36

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC



*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 of 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

37



# Kitchen Sink Summary

38

## Kitchen Sink Summary - 1

**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



39

## Kitchen Sink Summary - 2



**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

40

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**

*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC

## Kitchen Sink Summary - 3

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



41



## Questions?

**Stacey Rose, MD, FACP, FIDSA**
**srrose@bcm.edu**

**OL15 Kitchen Sink: Syndromes Not Covered Elsewhere – Bonus Cases**
*Speaker: Stacey Rose, MD*

©2026 Infectious Disease Board Review, LLC