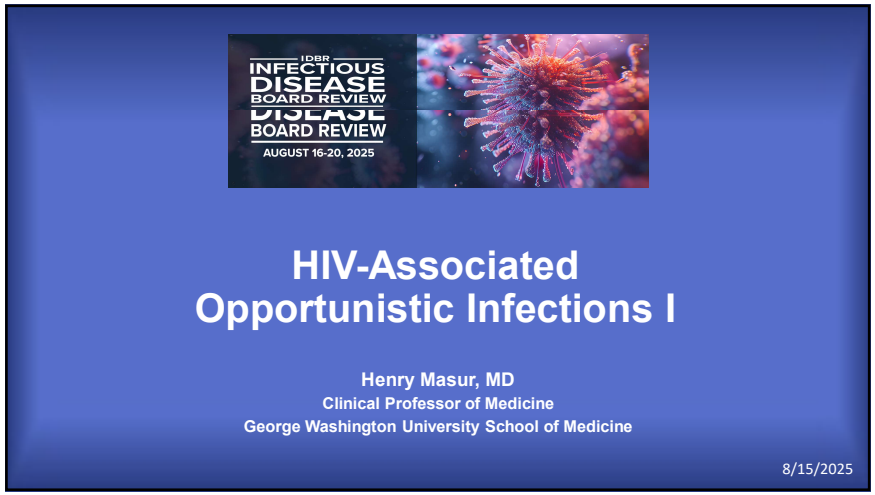
34 HIV-Associated Opportunistic Infections I

Speaker: Henry Masur, MD



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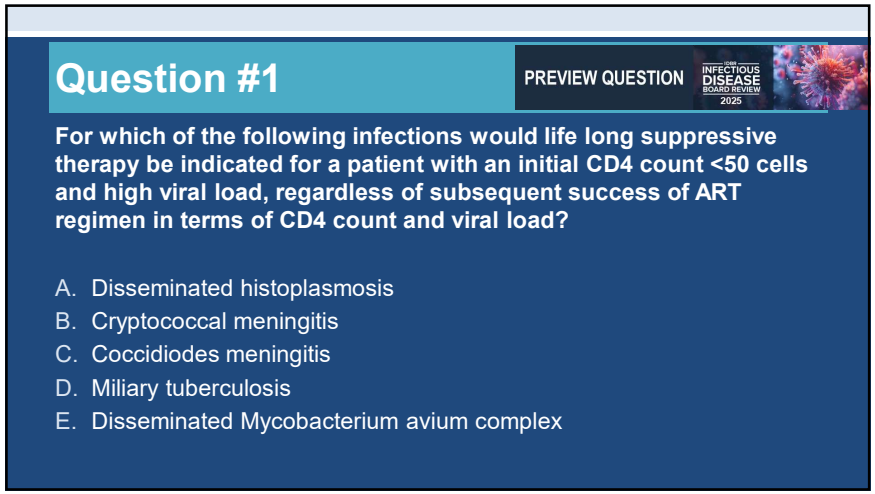

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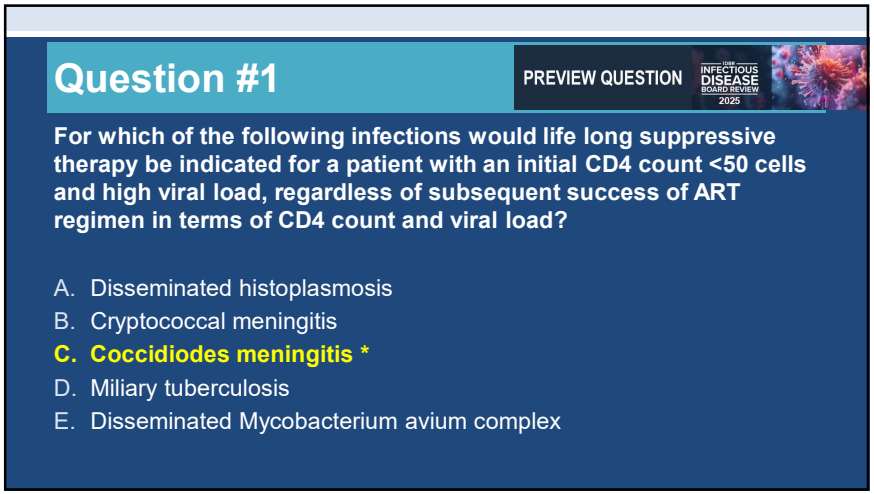

4

Question #2

PREVIEW QUESTION

A patient who was recently found to be HIV positive…

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

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

Otherwise, he felt fine.

5

Question #2

PREVIEW QUESTION

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

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

6

Question #2

PREVIEW QUESTION

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

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

7

Question #3

The patient whose photo is shown:

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

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

8

Question #3

The patient whose photo is shown:

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

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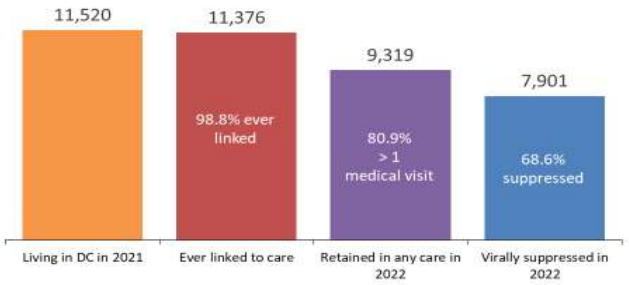
9

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

10

HIV Care Continuum, Washington DC
2023 Annual Report



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

11

Clinical Indicators of Immunosuppression

Mucosal Candida

Oral Hairy Leukoplakia (EBV)

Dermatomal Zoster

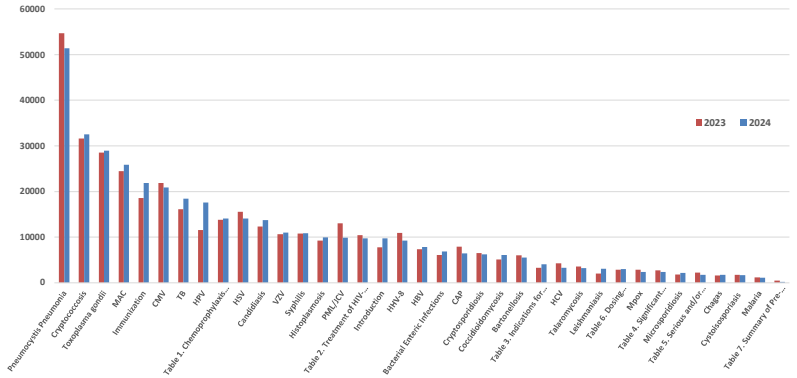
12

Cardinal AIDS-Defining Illnesses

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

13

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



14

Susceptibility to Opportunistic Infections Patients with HIV

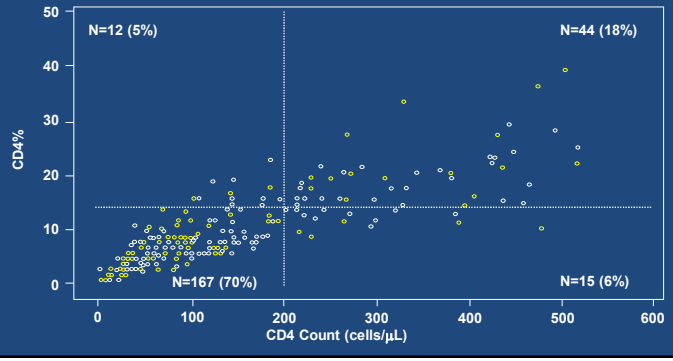
- **CD4 Count**
  - Current count is most important
  - Prior nadir count is much less important
- **Viral Load**
  - Independent risk factor for OIs

15

At What CD4 Counts Do Opportunistic Infections Occur?

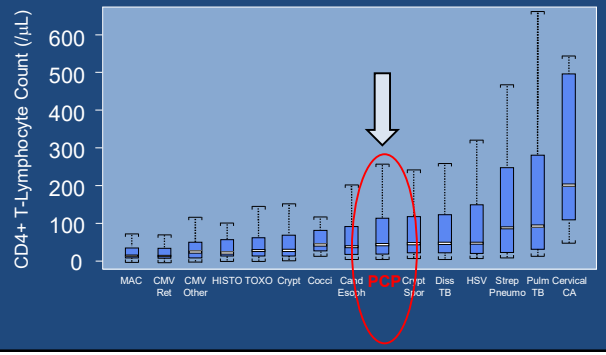
16

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



17

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



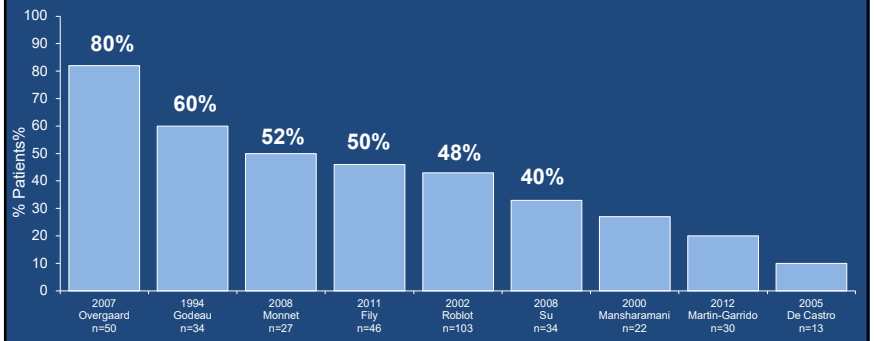
18

Warning for Utility of CD4 Counts in Non-HIV

- High CD4 Count (e.g.,>200) NOT indicative of "low risk"
- Low CD4 Count (e.g.,<200) probably indicates "high risk"

19

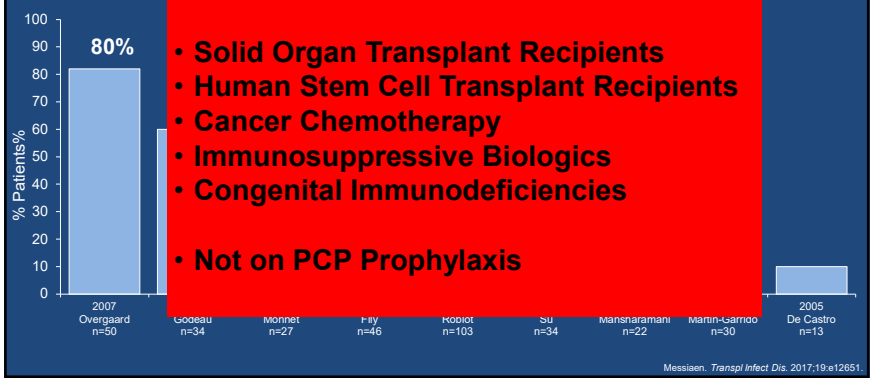
Non-HIV Patients Who Develop PCP When CD4>200



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

20

Non-HIV Patients Who Develop PCP When CD4>200



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

21

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

22

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

Antiretroviral Therapy

23

When to Start ART Following Opportunistic Infection

24

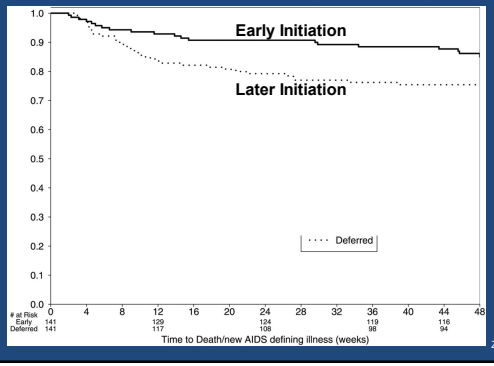
When to Start ART Following Opportunistic Infection

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

25

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

Survival Without Additional OI



Zolopa PLoS One 2009;4:e5575

26

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

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

*For TB meningitis: potentially longer

27

Primary and Secondary OI Prophylaxis
These Are Guidelines But They Are Based on 1980-1990 ART

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

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

28

Discontinue Prophylaxis/Chronic Maintenance

Board might consider this a "look up"

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

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

29

30

Contraindicated Vaccines for Persons With HIV

For CD4 T lymphocyte (CD4) cell count <200 cells/mm^3:
- Measles
- Mumps
- Rubella
- Varicella (VAR)
- Live attenuated typhoid Ty21a
- Yellow fever

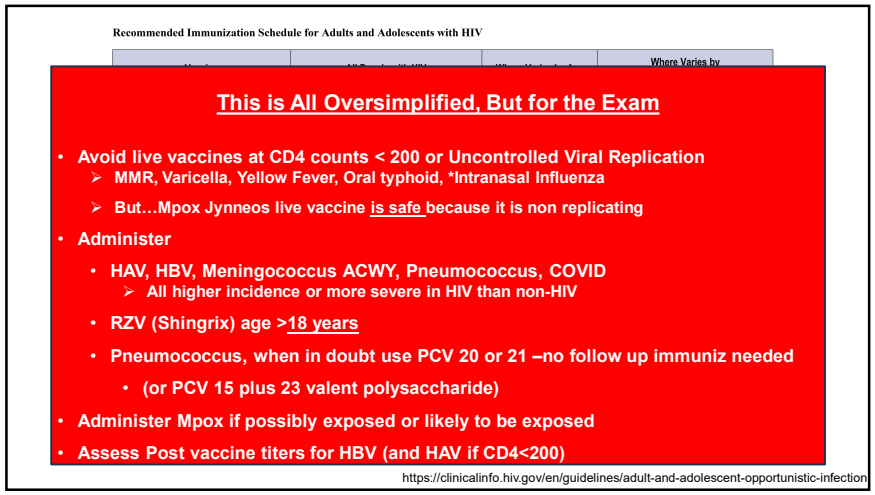
For any CD4 counts:
- Live attenuated influenza vaccine (LAIV)
- Live attenuated smallpox vaccine (ACAM2000)

31

Vaccines with Specific Recommendations Related to HIV Status

- COVID-19
- Hepatitis A (HAV)
- Hepatitis B (HBV)
- Meningococcus serogroup A, C, W, Y (MenACWY)
  - Repeat every 5 years
- Pneumococcal vaccines
- Human papillomavirus
- Zoster: Immunize at age >=18 years

32



33

Who Should be Vaccinated for HBV

- People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL)
- Current Recommendation
  - Two dose regimen*
    - Conjugated vaccine: Heplisav-B® IM at 0 and 1 months
  - NIH/IDSA perspective re assessing post vaccine titers
    - 1-2 months post vaccine and then some experts would test annually
    - Boost responders when annual level <10mIU/ml
    - *BEe-HIV Trial is too new for exam-HIV and prior nonresponse (Jama 7/25)-

34

HBV Non-Responders

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

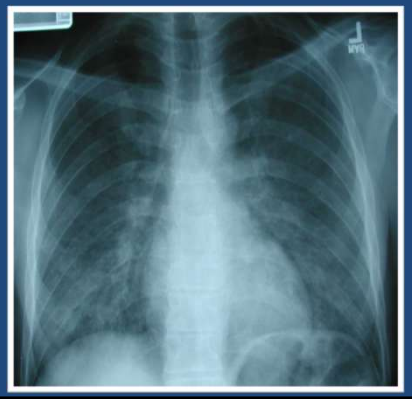
35

HBV Immunization for Persons with Isolated Anti HBc

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

36

HIV Associated Pulmonary Disease



37

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

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

38

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

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

39

Approach to Diagnosis and Therapy of Pneumonia in PWH

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

40

Etiology of HIV Associated Pulmonary Disorders

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

41

Pneumococcal Disease in Persons with HIV Infection

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

42

Internal Medicine Question

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

43

Strategies to Reduce Incidence of Pneumonia for Patients with HIV

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

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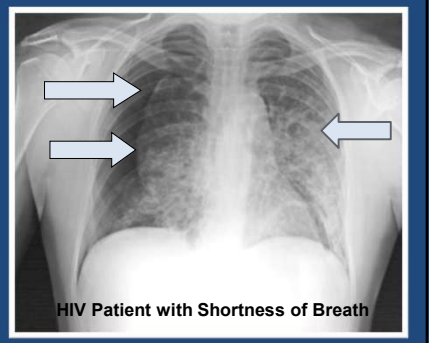
HIV and Covid

- **No increased susceptibility**
- **Probably increased severity, especially with low CD4**
  - **May be primarily linked to other co-morbidities**
- **Drug interactions**
  - **Paxlovid and Remdesivir**
    - **No major interaction with Integrase inhibitors or Cobicistat**

45

Question #4

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


HIV Patient with Shortness of Breath

46

Question #4

What is the most likely INFECTIOUS cause of this pneumothorax?

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

47

Question #4

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C. PCP *
D. CMV
E. Aspergillosis

48

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

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

49

Host Susceptibility to PCP

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

50

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

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

Kovacs et al. Ann Intern Med 1984

51

Uncommon Manifestations of PCP



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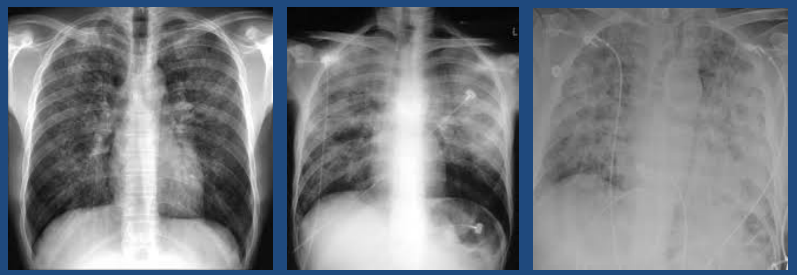
HIV Related PCP



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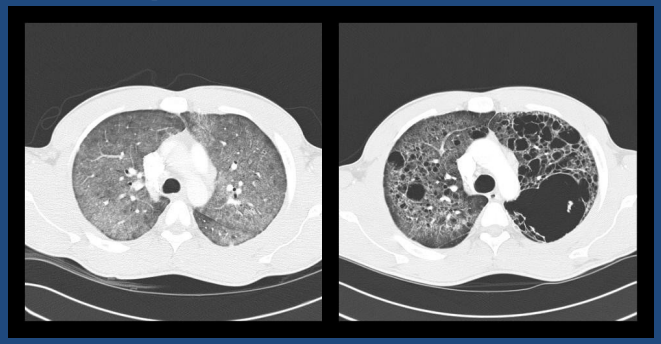
Development of Pneumatocoeles



May 23 June 13

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Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

55

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

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Diagnosis of Pneumocystis Pneumonia

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

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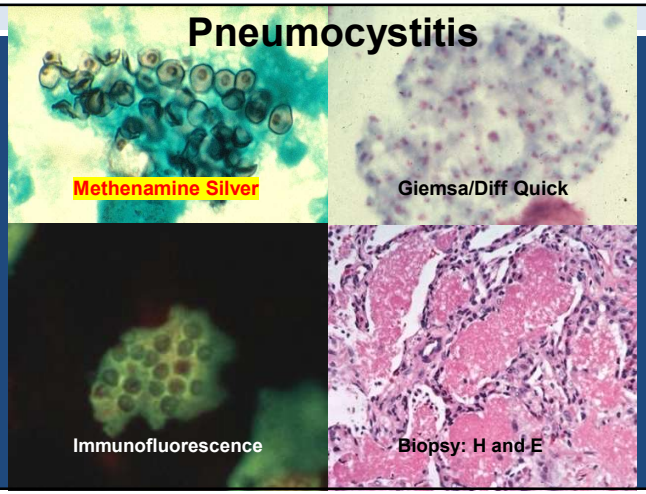
Pneumocystitis



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PCR
Diagnosis of Pneumocystis
Bronchoalveolar Lavage or Sputum

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

59

PCR
Diagnosis of Pneumocystis
Bronchoalveolar Lavage or Sputum

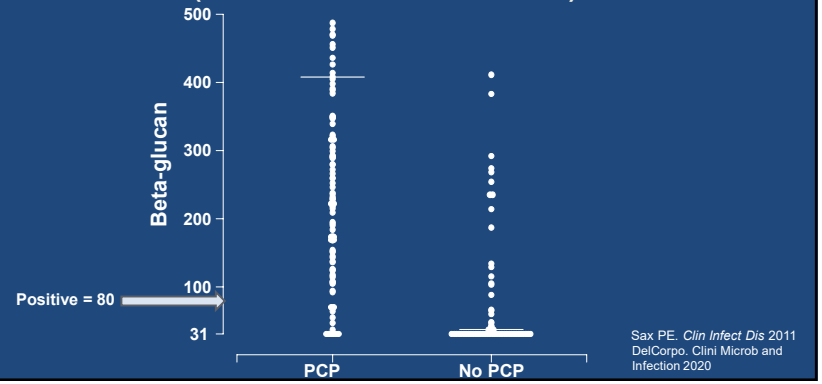
- High
  - Ins
- High
  - Po
  - Cy

Negative BAL PCR rules out PCP

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

60

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



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

61

Question #5

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

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

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

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

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

62

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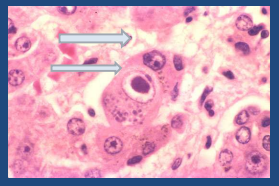
63

CMV and Lungs



Eosinophilic Intranuclear Inclusion and Basophilic Cytoplasmic Inclusions

CMV almost never causes pneumonia …In PWH

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

64

Question #6

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

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

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

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

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

65

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C. Fluconazole interaction with another drug
D. Dapsone *
E. Dolutegravir

66

Two Pharmacologic Issues To Watch For

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

67

Therapy for HIV Related Pneumocystis Pneumonia

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

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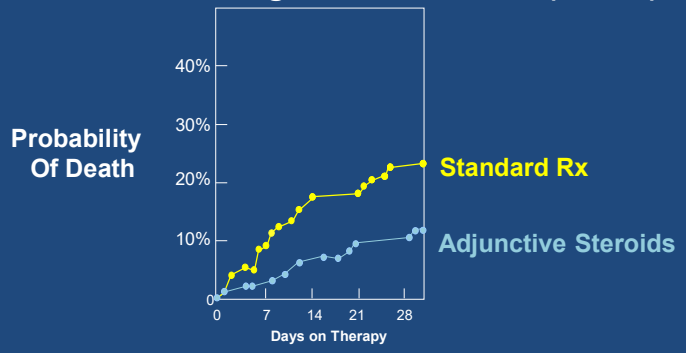
Likelihood of Death in Patients with Moderate-Severe PCP Receiving Corticosteroids (n=251)



(Bozette, NEJM 5/90)

69

How to Manage Patients Who Are Failing TMP-SMX

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

70

Reasons to Deteriorate During Treatment for PCP

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

71

Reasons to Deteriorate During Treatment for PCP

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

Patients Failing TMP-SMX Not Testable!

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

72

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

73

Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

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

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Toxicity and Other Considerations Regarding Antipneumocystis Therapy

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

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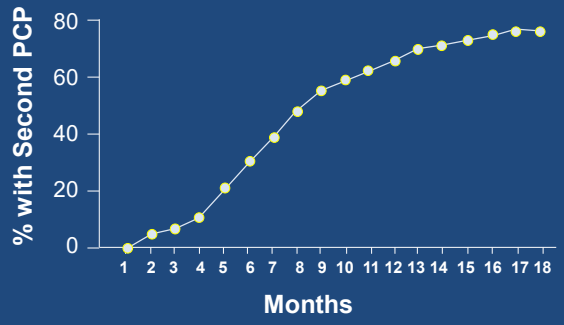
Without ART or Chemoprophylaxis Second Episodes of HIV Associated PCP Are Amazingly Common



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Indications for Primary and Secondary PCP Prophylaxis

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

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

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

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Primary or Secondary Prophylaxis for Pneumocystis Pneumonia

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

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Thank You!

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