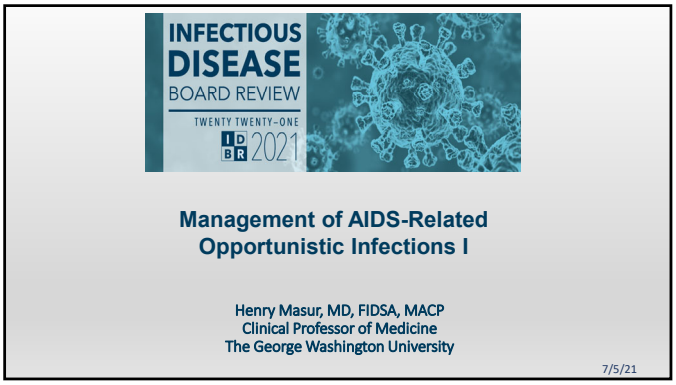
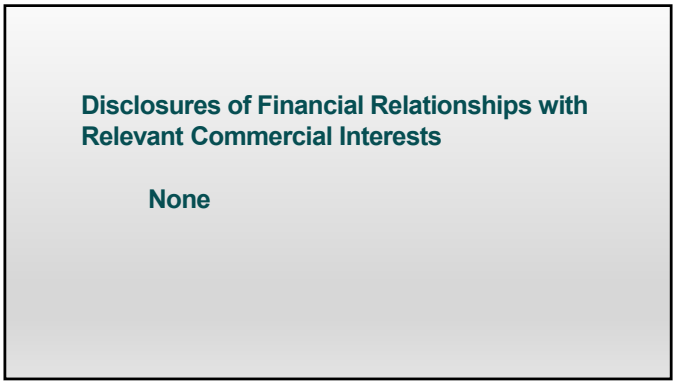
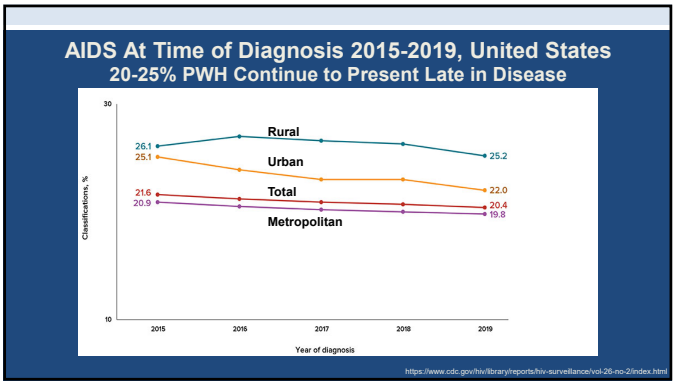
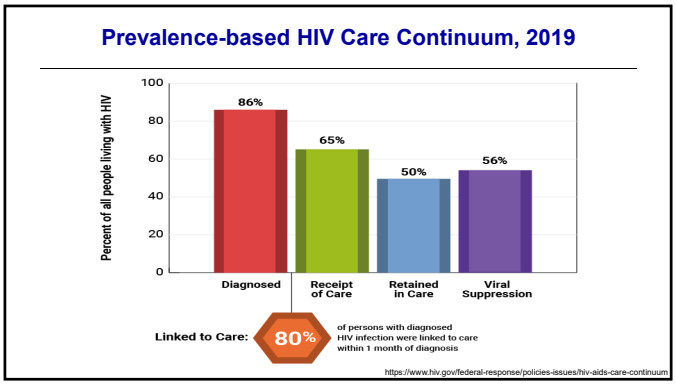
28 – HIV Associated Opportunistic Infections I

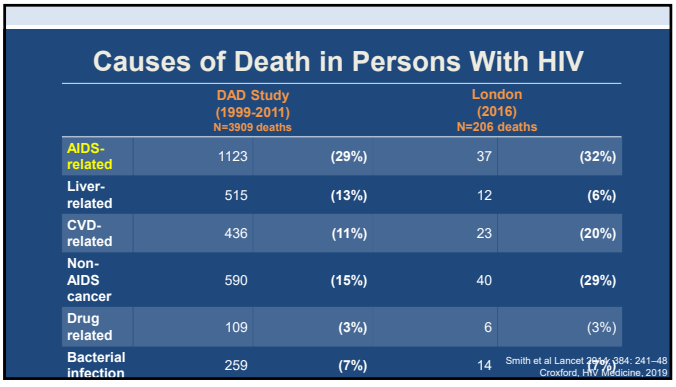
Speaker: Henry Masur, MD

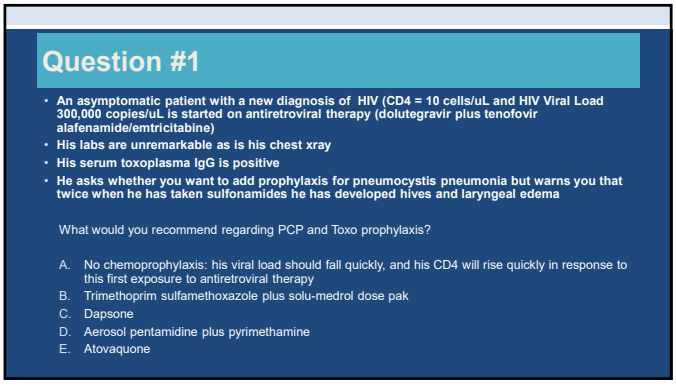












28 – HIV Associated Opportunistic Infections I

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Question #2

The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

He has had low grade fevers for several months.

For your differential diagnosis, what besides Kaposi sarcoma would be the most likely cause of these lesions and their associated fever?

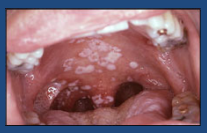
Question #2

Question #2

The most likely cause of these skin lesions, if they are not Kaposi sarcoma, is:

A. HHV-6
B. CMV
C. Cryptococcus neoformans
D. Bartonella
E. Rhodococcus

Clinical Indicators of Immunosuppression



Cardinal AIDS-Defining Illnesses

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

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**

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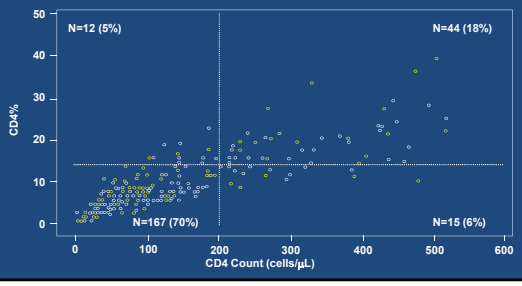
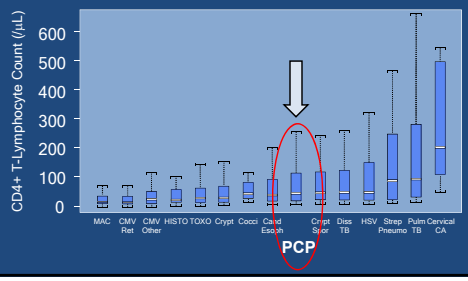
At What CD4 Counts Do Opportunistic Infections Occur?

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



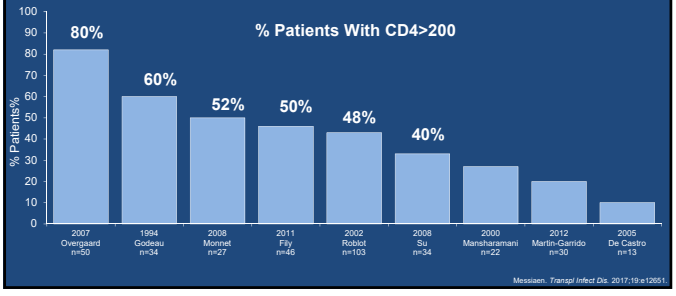
CD4+ Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS



CD4 Counts in NON-HIV Patients

- **Low CD4 Count**
  - Susceptible to PCP
- **High CD4 Count**
  - Not necessarily protected from PCP

WARNING For Non-HIV Patients CD4 Count Are Not A Sensitive Indicator of PCP



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

What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplams Regardless of CD4 Count and Viral Load?

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What is the Most Effective Intervention to Prevent Opportunistic Infections and Neoplams Regardless of CD4 Count and Viral Load?

Antiretroviral Therapy

When to Start ART Following Opportunistic Infection

When to Start ART Following Opportunistic Infection

- Most OIs
  - –Within 2 weeks of diagnosis

When to Start ART Following Opportunistic Infection

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

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, new positive cocci IgM or IgG
  - – ~~MAC (CD4 < 50)~~ ---NIH/CDC/IDSA guideline has eliminated this
  - – ~~•~~
- 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

Prophylaxis NOT Routinely Recommended in US

Primary	Secondary
• Candida	Candida*
• Cryptococcus	
• HSV	HSV*
• VZV	VZV*
• CMV	
• MAC	

*Secondary Prophylaxis would be reasonable if recurrences were frequent or severe

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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*

Primary Coccidiomycosis Prophylaxis 2021 OI Guideline

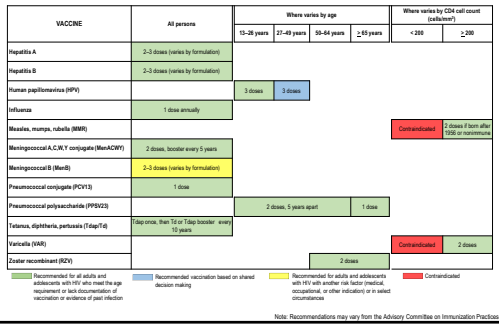
Testing

- Once or twice yearly testing for seronegative patients

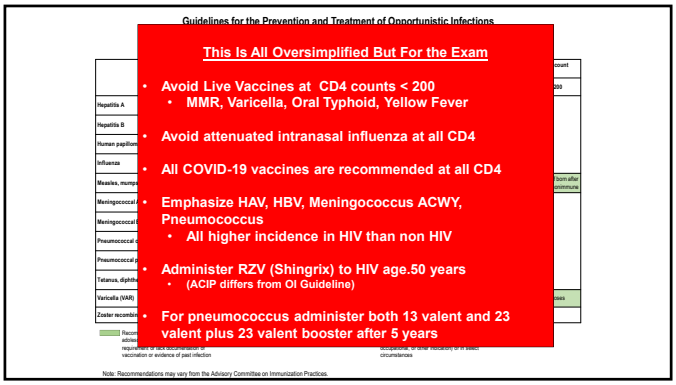
Primary Prophylaxis

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

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV



Note: Recommendations may vary from the Advisory Committee on Immunization Practices.



Who Should be Vaccinated for HBV

- Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs <10 international units/mL)
- Patients with isolated anti-HBc and negative HBV DNA
  - Vaccinate with one standard dose of HBV vaccine and check anti-HBs titers 1 to 2 months afterward
  - If the anti-HBs titer is ≥100 IU/mL, no further vaccination is needed
  - If the titer is <100 IU/mL, then complete series of HBV vaccine (single-dose or double-dose) followed by anti-HBs testing
  - If titers are not available, then give complete vaccine series
- Note
  - In patients with low CD4 cell counts, vaccination should not be deferred until CD4 count reaches >350 cells/μL, because some patients with CD4 counts <200 cells/μL do respond to vaccination

Who Are HBV Non Responders

- Definition
  - • Anti-HBs <10 international units/mL 1 month after vaccination series
- Options: Not testable
  - Switch to other recombinant vaccine, ie GSK to Merck or vice versa
  - Double dose of recombinant vaccine
  - Four dose regimen
  - Heplisav adjuvant vaccine

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Post Exposure to HBV for PWH

- **Prior vaccine with documented response**
  - Nothing needed
- **Prior vaccine with NO response measured**
  - Administer single dose
- **No prior vaccine**
  - HBIG if within 7 days of percutaneous and 14 days of sexual exposure
    - Might not be necessary for patients on tenofovir or lamivudine
  - Full vaccine series simultaneously with HBIG
  - https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm

HIV Associated Pulmonary Disease

Etiology of HIV Associated Pulmonary Disorders

Common	Uncommon	Rare
• Pneumococcus	• Aspergillus	• CMV
• Hemophilus	• Histo/Cocci	• MAC
• Pneumocystis	• Staphylococci	• HSV
• Tuberculosis	• Toxoplasma	
• "Atypicals/viral"	• Lymphoma	
	• Kaposi sarcoma	

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)**

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)**

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
• Xray	Suggestive But Never Diagnostic

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Speaker: Henry Masur, MD

Pneumococcal Disease in Persons with HIV Infection

- **CD4<200**
  - Frequency enhanced
  - Severity/Extrapulmonary Complications Enhanced
- **CD4>350**
  - Frequency: Enhanced
  - Severity: No difference
- **Comorbidities Predisposing to Pneumococci Over-Represented in HIV**
  - Opioid Use Disorder, Etoh, Tobacco, Lack of Immunization
  - COPD, CHF, Obesity, MRSA colonization, Liver Disease

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

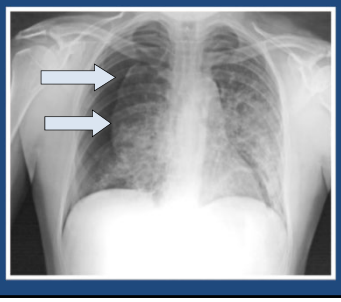
Strategies to Reduce Incidence of Pneumonia for Patients with HIV

- **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

Question #3

- **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 no unusual exposures.**
- **The most likely INFECTIOUS cause of this pneumothorax is:**

HIV Patient with Shortness of Breath



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The patient lives in Chicago, works in an office and has never left the Midwest and no unusual exposures.

The most likely INFECTIOUS cause of this pneumothorax is:

A. Cryptococcosis
B. Blastomycosis
C. PCP
D. CMV
E. Aspergillosis

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Pneumocystis Jirovecii (Formerly *P. carinii*)

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

Host Susceptibility to PCP

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

Clinical Features of PJP in Pre-AIDS Era, (n=168)

No Feature is Present 100% of Initial Presentations

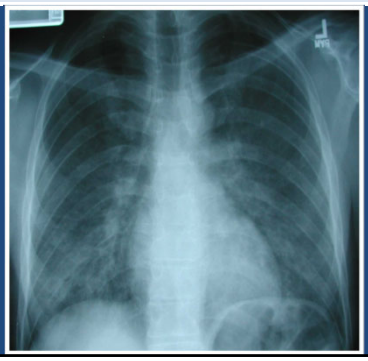
Symptom	% Patients
• Dyspnea	91%
• Fever	66%
• Cough	47%
Productive	7%
Non-productive	40%
• Signs	
– Cyanosis	39%
– Rales	33%

Walzer, Ann Intern Med 1974

Uncommon Manifestations of PCP

Imaging of PCP

- **Early-CT is never normal!**
  - Reticular (interstitial)
  - Nodular (interstitial)
  - Ground Glass (sparing periphery)
- **Later-Progression from Interstitial**
  - Consolidation (late finding)
  - Upper Lobe Cysts (thin walled)
  - Pneumothorax
    - (cyst and bronchopleural fistula)



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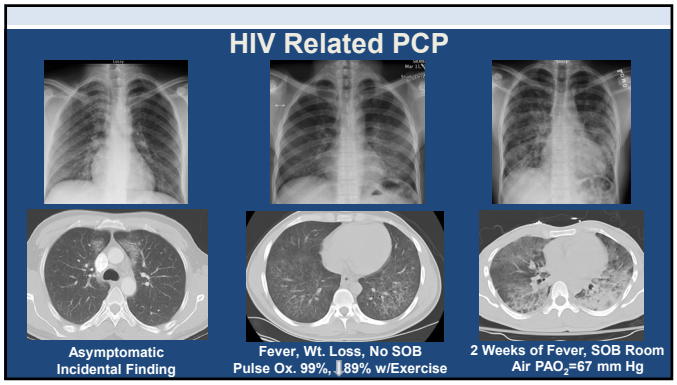
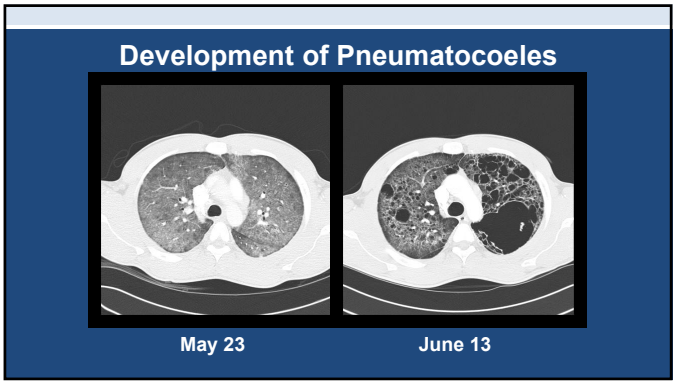




Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

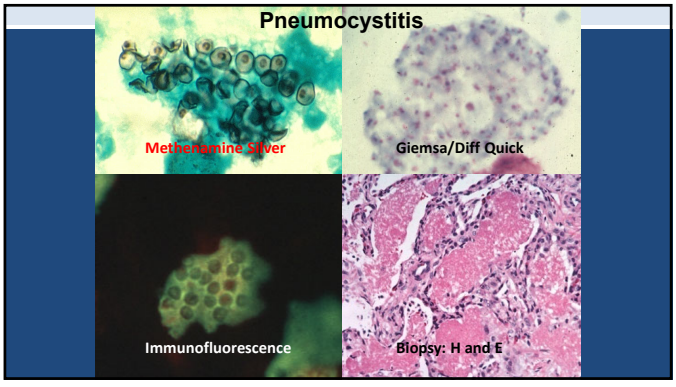
- **Most Frequent**
  - **Diffuse symmetric interstitial infiltrates progressing to diffuse alveolar process**
    - **Butterfly pattern radiating from hilum**

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **Other Patterns Recognized**
  - **(Other concomitant infectious or neoplastic disease processes?)**
  - **Lobar infiltrates**
  - **Upper lobe infiltrates**
  - **Pneumothorax**
  - **Solitary nodules**
  - **Cavitating lesions**
  - **Infiltrates with effusions**
  - **Asymmetric or unilateral processes**
  - **Normal chest x-ray**

Diagnosis of Pneumocystis Pneumonia

Specimen Acquisition		Organism Detection
Open lung biopsy	1957	Methenamine silver
Transbronchial biopsy	↓	Immunofluorescence
Bronchoalveolar lavage		Giemsa / Diff Quik
Induced sputum	2021	PCR



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PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **Highly sensitive in BAL**
  - Not useful in blood/serum/plasma
- **High biologic specificity**
  - Positive result might be infection or disease
  - Cycle number (copy number)helpful but not definitive

PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- **High**
  - No
- **High**
  - Po
  - Cy

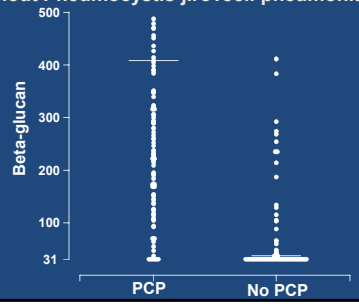
Negative BAL PCR rules out PCP

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

Is There A Serologic Test for PCP?
No!

- **Serum Antibody or PCR Test**
  - Not useful…yet
- **LDH**
  - Sensitivity depends on severity
  - Non-specific-elevated in many lung diseases
- **Beta Glucan**
  - Sensitive but not specific
  - Maybe useful for
    - Heightened suspicion of PCP if BAL or sputum not feasible
    - Following response to Rx

Distribution of β-glucan Results at Baseline in Those With and Without Pneumocystis jirovecii pneumonia (PCP)



Sax PE. *Clin Infect Dis* 2011

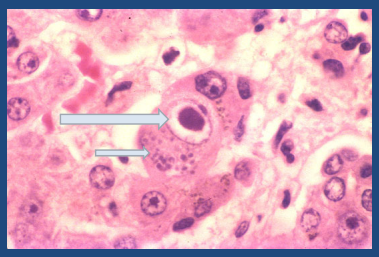
Question #4

- **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 cytology lab reports several CMV inclusion bodies in the BAL.**

The best course of action in addition to considering antiretroviral therapy would be:

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, ie continue TMP-SMX alone

CMV Cytology



Eosinophilic Intranuclear Inclusion and Coarse Basophilic Cytoplasmic Inclusions

CMV Almost Never Causes Pneumonia In HIV Infected Pts

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Question #4

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

Ten days later the patient returns with headache, shortness of breath, a normal chest CT

Pulse oximetry shows an O2 saturation of 85%

A stat ABG is ordered which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 96%.

The ABG lab reports methemoglbinemia = 25%

The most likely cause of this patient's syndrome is:

A. Pneumocystis pneumonia
B. Pulmonary Kaposi sarcoma
C. Fluconazole interaction with another drug
D. Dapsone
E. Clarithromycin

Question #4

A patient with HIV infection newly diagnosed (CD4=10, VL= 200,000 copies/uL) was started on the following medications: efavirenz, emtricitabine, tenofovir, dapsone, clarithromycin. Fluconazole was added when oral thrush was noted.

Ten days later the patient returns with headache, shortness of breath, a normal chest CT

Pulse oximetry shows an O2 saturation of 85%

A stat ABG is ordered which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 80%.

The ABG lab reports Methemoglobin at 25%

The most likely cause of this patient's syndrome is:

A. Pneumocystis pneumonia
B. Pulmonary Kaposi sarcoma
C. Fluconazole interaction with another drug
D. Dapsone
E. Clarithromycin

Answer #4

Methemoglobemia = Methemoglobin>3%

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

Answer #4

Methemoglobemia = Methemoglobin>3%

Unlike normal hemoglobin, methemoglobin does not bind oxygen and as a result cannot deliver oxygen to the tissues

Symptoms: Headache to dyspnea to delirium and organ ischemia to death start occurring at methg >10%; >30% is life threatening

Detection
Too complicated for IDBR due to improving technology
Many systems measure methemoglobinemia directly
look for high P02, low O2 Sat and…report of methemoglobin

Causes: Many: Dapsone and topical anesthetics notorious
Also chloroquine, primaquine, sulfa, nitrofurantoin

Therapy: Stop drug +/- methylene blue, ascorbic acid, transfusions

Question #5

A 50-year-old male with HIV and PCP is receiving pentamidine 4 mg/kg IV over 1 hr qd.

On the ninth day of therapy, while awaiting transportation home, he has a syncopal episode.

An EKG done by the code team is normal.

What Non cardiac toxicity of pentamidine would be most likely

A. Hyponatremia
B. Seizure
C. Hypoglycemia
D. Hypertensive crisis and stroke
E. Pulmonary embolus

Therapy for 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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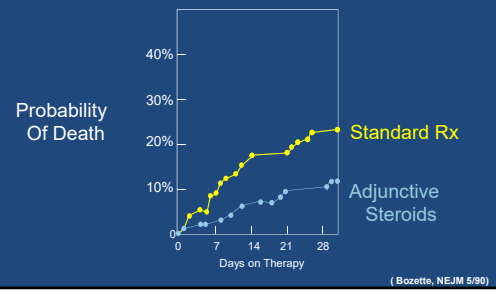
Speaker: Henry Masur, MD

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



(Bozette, NEJM 5/90)

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine

A Question That Could Be on Boards

- What drugs should only be given after screening for Glucose-6-Phosphate Dehydrogenase
  - G6PD is common and nationality is increasingly difficult to define as a predictor
  - Males have more severe hemolysis since this is X linked
- Presentation
  - Hemolysis, jaundice, back and abdominal pain 2-4 days post drug exposure
  - Smear shows hemolytic pattern and "Heinz bodies"
  - Hemoglobinuria, high retic count
- Drugs
  - Primaquine
  - Dapsone
  - And…..fluoroquinolones, Nitrofurantoin, Nalidixic acid, tafenoquine
- Screening
  - Qualitative assay is used in urgent situations before drug administration
    - Testing after hemolysis can be misleading
  - Other management issues are too complicated for ID boards

How to Manage Patients Who Are Failing TMP-SMX

- Average Time to Clinical Improvement
  - 4-8 Days
- Radiologic Improvement
  - Lags clinical improvement

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)

Reasons to Deteriorate During Treatment for PCP

- Fluid overloa
  - Iatrogenic, ca… entamidine related)
- Anemia
- Methemoglob
  - Dapsone, prin
- Pneumothora
- Unrecognize
- Immune Rec

Patients Failing TMP-SMX Not Testable!

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

28 – HIV Associated Opportunistic Infections I

Speaker: Henry Masur, MD

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

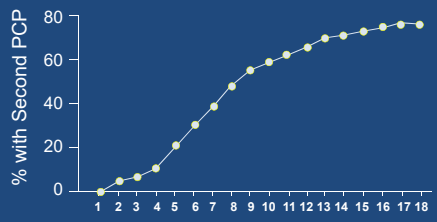
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

Drug	Toxicities
TMP-SMX	↓WBC, ↓plat, ↑LFT, ↑Creat, ↑Amylase, rash, fever, pruritus, "Sepsis" syndrome-distributive shock Hyperkalemia (TMP) Cross reactivity: dapsone (± 50%)
Pyrimethamine-Sulfadiazine	Similar to TMP-SMX Folinic acid necessary (not folate) to prevent cytopenias

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

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: CD4 100-200 and VL<50 x 3M)
Restart	CD4<200 cells/µL

Whether prophylaxis is needed at CD4 100-200 with suppressed viral load is too controversial for exam

Primary or Secondary Prophylaxis Agents for Pneumocystis Pneumonia

- **First Choice**
  - TMP-SMX
- **Other Options**
  - Aerosol pentamidine **OR**
  - Atovaquone **OR**
  - (Monthly IV pentamidine) **OR**
  - (Dapsone)

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