35 – HIV Associated Opportunistic Infections I

Speaker: Henry Masur, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

HIV-Associated Opportunistic Infections I

Henry Masur, MD, FIDSA, MACP
Bethesda, Maryland

7/1/2024

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Question #1

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

1. Disseminated histoplasmosis
2. Cryptococcal meningitis
3. Coccidiodes meningitis
4. Miliary tuberculosis
5. Disseminated Mycobacterium avium complex

Question #2

PREVIEW QUESTION

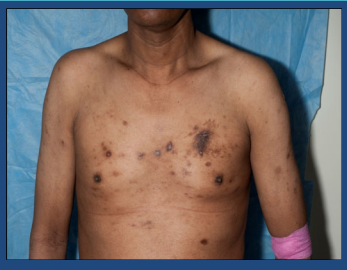
The patient whose photo is shown is HIV positive (CD4=10 cells/uL, VL=2 mil copies) and has noted these lesions developing on his trunk, face and extremities over the past 8 months.

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

PREVIEW QUESTION



Question #2

PREVIEW QUESTION

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

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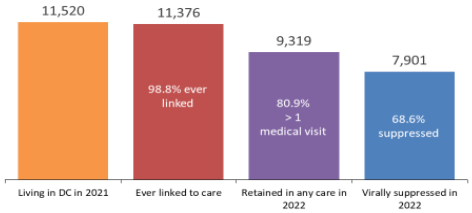
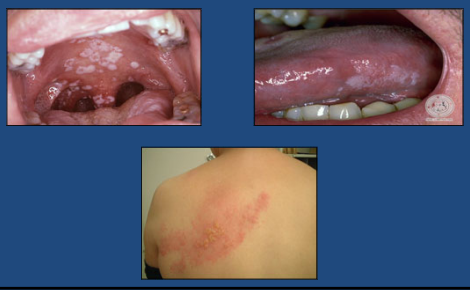
Why Does Anyone in US Develop an HIV Associated Opportunistic Infection in Current Era?

HIV Care Continuum, Washington DC
2023 Annual Report



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

Clinical Indicators of Immunosuppression



Cardinal AIDS-Defining Illnesses

- **Pneumocystis pneumonia**
- **Cryptococcus**
- **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

At What CD4 Counts Do Opportunistic Infections Occur?

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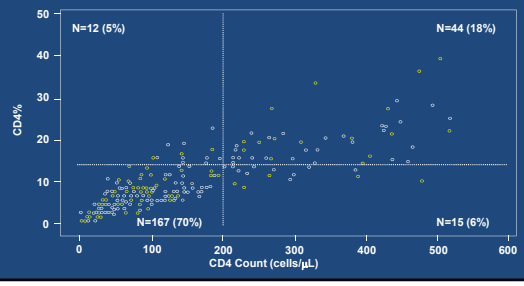
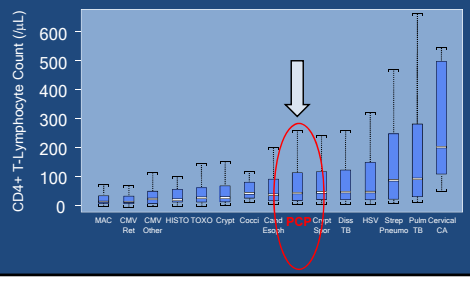
Scatterplot of CD4 Number vs CD4 Percent Within 6 Months of HIV-Associated PCP



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

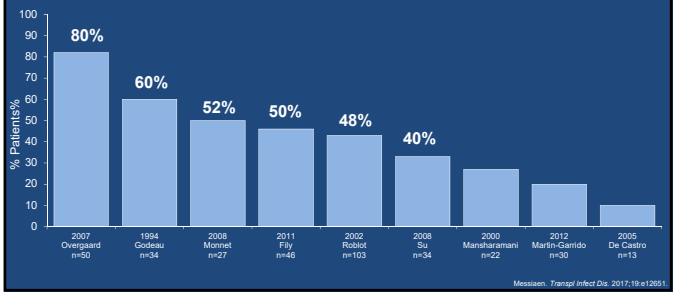


Warning for Utility of CD4 Counts in Non HIV

•

CD4 Count Are Not A Sensitive Indicator of PCP

% Non HIV Patients With PCP When CD4>200



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

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

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Antiretroviral Therapy

CD4 Count

Viral Load

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When to Start ART Following Opportunistic Infection

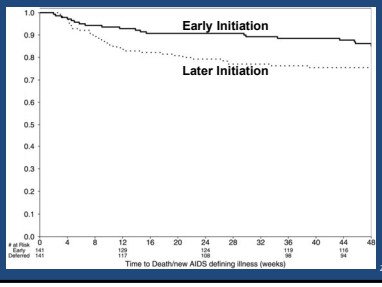
When to Start ART Following Opportunistic Infection

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

ART Initiation Following HIV Related Opportunistic Infections

Early Initiation (<2 weeks) Favors Survival

Survival Without Additional OI



Zolopa PLoS One 2009;4:e5575

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

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 cant 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)

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*

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Discontinue Prophylaxis/Chronic Maintenance

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

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

Primary Coccidiomycosis Prophylaxis 2024 OI Guideline

SerologicTesting

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

Primary Prophylaxis

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

Recommended Immunization Schedule for Adults and Adolescents with HIV

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

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

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

Recommended Immunization Schedule for Adults and Adolescents with HIV

This is All Oversimplified, But for the Exam

- **Avoid live vaccines at CD4 counts < 200 or Uncontrolled Viral Replication**
  - **MMR, Varicella, Yellow Fever, Oral typhoid, *Intranasal Influenza**
  - **Mpox Jynneos live vaccine is safe because it is non replicating**
- **Administer**
  - **HAV, HBV, Meningococcus ACWY, Pneumococcus, COVID**
    - **All higher incidence or more severe in HIV than non HIV**
  - **RZV (Shingrix) age >18 years**
  - **Pneumococcus, when in doubt use PCV 20**
    - **(or PCV 15 plus 23 valent polysaccharide)**
- **Administer Mpox if possibly exposed or likely to be exposed**
- **Assess Post vaccine titers for HBV (and HAV if CD4<200)**

Slide 28

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

Who Should be Vaccinated for HBV

- **People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL)**
  - **The specific regimens are too granular and changing to likely be on exam**
    - **Preferred by some: two dose regimen**
      - **Vaccine conjugated to HepBCpG (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**

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

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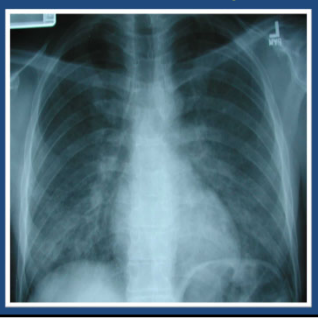
HBV Immunization for Persons with Isolated Anti HBc

- **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

HIV Associated Pulmonary Disease



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

Etiology of HIV Associated Pulmonary Disorders

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

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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

Internal Medicine Question

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

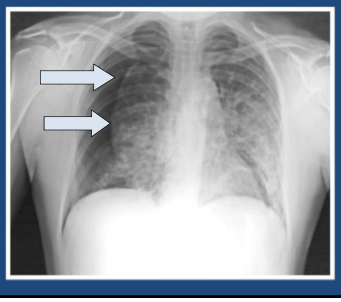
HIV and Covid

- No increased susceptibility
- Probably increased severity
  - May be primarily linked to other co-morbidities
- Drug interactions
  - Integrase inhibitors and Cobicistat and Ritonavir contain regimens likely OK with Paxlovid
  - ART and Remdesivir no interactions

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

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

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

Host Susceptibility to PCP

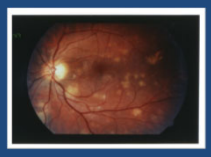
- CD4 < 200 cells/μL --(90% of cases)
- CD4% <14

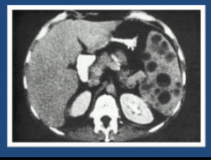
PCP is More Subacute in Persons With HIV Than Other Immunosuppressed Persons

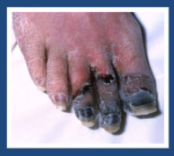
Sign or Symptom	HIV (n=48)	Non-HIV (n=38)
Symptom		
Fever	81%	87%
Cough	81%	71%
Shortness of breath	68%	66%
Duration of symptoms,	28 days	5 days
Temp> 38°C	76%	92%
PaO_2	69 mm Hg	52 mm Hg
A-a gradient	41 mm Hg	59 mm Hg
% with normal ABG	5-20%	

Kovacs et al. Ann Intern Med 1984

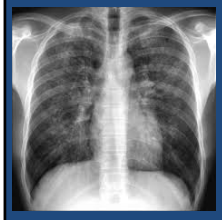
Uncommon Manifestations of PCP

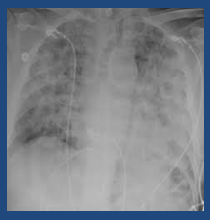






HIV Related PCP





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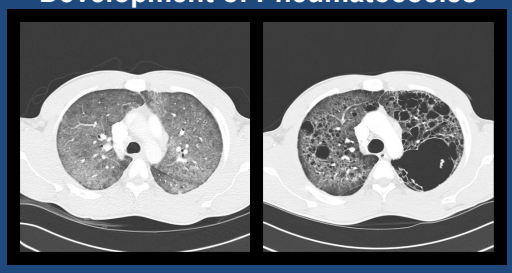
Development of Pneumatocoeles



May 23 June 13

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

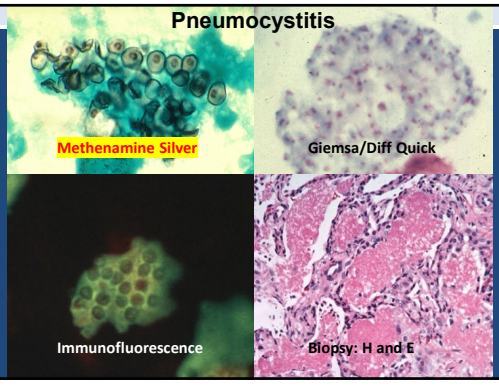
- Other Patterns Recognized
  - (Other concomitant infectious or neoplastic disease processes?)
  - Lobar infiltrates
  - Upper lobe infiltrates
  - Pneumothorax
  - Solitary nodules
  - Cavitating lesions
  - Infiltrates with effusions
  - Asymmetric or unilateral processes
  - Normal chest x-ray

Diagnosis of Pneumocystis Pneumonia

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

1957 → 2024

Pneumocystitis



PCR
Diagnosis of Pneumocystis
Bronchoalveolar Lavage or Sputum

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

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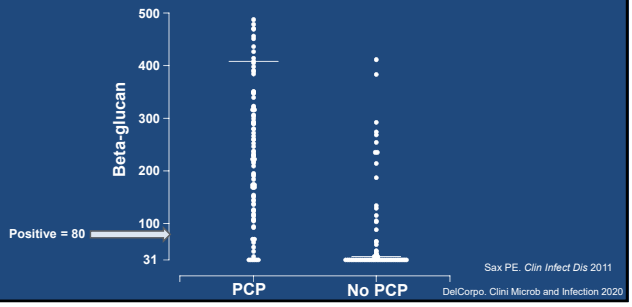
PCR
For Diagnosis of Pneumocystis in Bronchoalveolar Lavage

- High
  - No
- High
  - Po
  - Cy

Negative BAL PCR rules out PCP

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

Don't Use Beta Glucan Test for Diagnosis of PCP!!



Sax PE. *Clin Infect Dis* 2011

DelCorpo. Clini Microb and Infection 2020

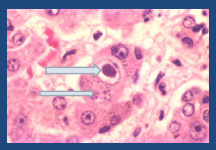
Question #4

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

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 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 more severe immunosuppression but not usually the cause of pneumonia…in this population

Question #5

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, dapsone, fluconazole.

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

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

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

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

Two Pharmacologic Issues To Watch For

- **Methemoglobinemia (>8-10%)**
  - 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
- **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

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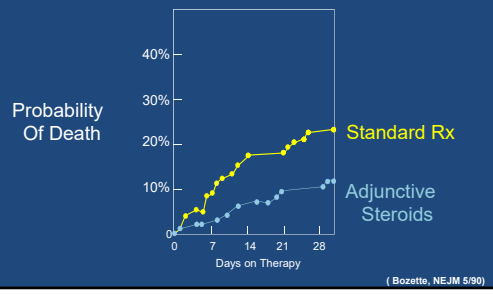
Therapy for HIV Related Pneumocystis Pneumonia

- **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**

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



(Bozette, NEJM 5/90)

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**

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, prim
- **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**

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

35 – HIV Associated Opportunistic Infections I

Speaker: Henry Masur, MD

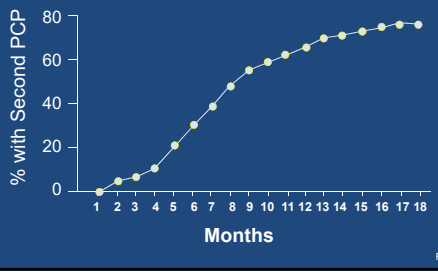
Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

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

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

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, ie cytopenia, renal dysfunction, transaminitis

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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