13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

Management of AIDS-Related Opportunistic Infections I

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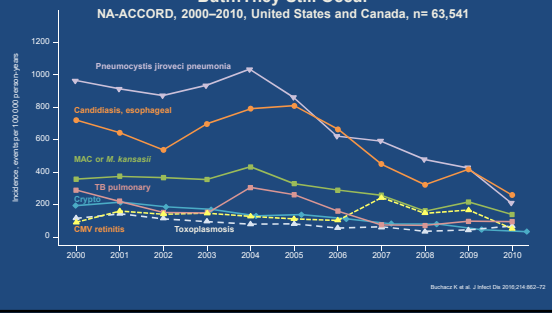
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Opportunistic Infections Among HIV Infected Persons Are Declining But…They Still Occur

NA-ACCORD, 2000–2010, United States and Canada, n= 63,541



Buchacz K, et al. J Infect Dis 2016;214:862–72

Question #1

- **An asymptomatic patient with a new diagnosis of HIV (CD4 = 10 cells/uL and HIV Viral Load 300,000 copies/uL is started on antiretroviral therapy (dolutegravir plus tenofovir alafenamide/emtricitabine)**
- **His labs are unremarkable as is his chest xray**
- **His serum toxoplasma IgG is positive**
- **He asks whether you want to add prophylaxis for pneumocystis pneumonia but warns you that twice when he has taken sulfonamides he has developed hives and laryngeal edema**

What would you recommend regarding PCP and Toxo prophylaxis?

A. No chemoprophylaxis: his viral load should fall quickly, and his CD4 will rise quickly in response to this first exposure to antiretroviral therapy
B. Trimethoprim sulfamethoxazole plus solu-medrol dose pak
C. Dapsone
D. Aerosol pentamidine plus pyrimethamine
E. Atovaquone

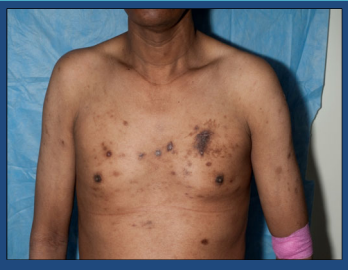
Question #2

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



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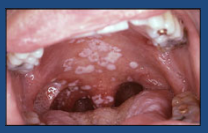
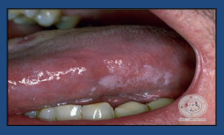
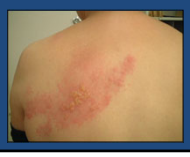
Question #2

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

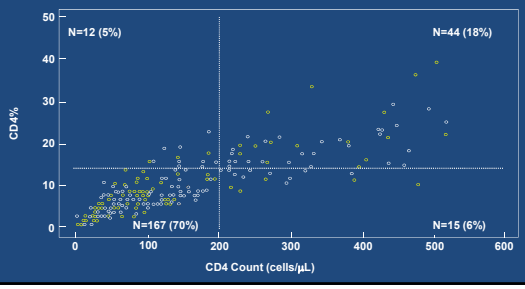
- **Pneumocystis pneumonia**
- **Toxoplasma encephalitis**
- **CMV Retinitis**
- **Disseminated Mycobacterium avium complex/Tuberculosis**
- **Chronic cryptosporidiosis/microsporidiosis**
- **Kaposi Sarcoma**

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

At What CD4 Counts Do Opportunistic Infections Occur?

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



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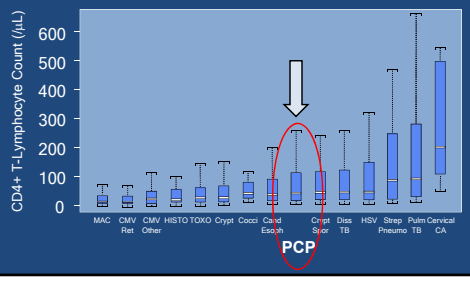
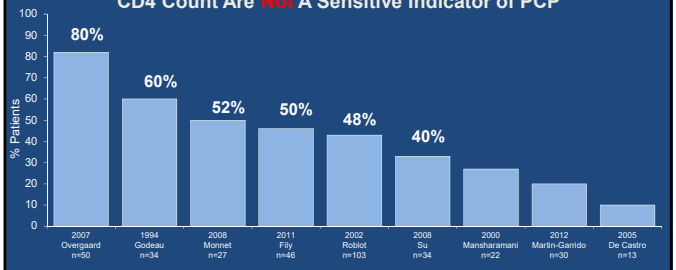
CD4+ Lymphocyte Counts Are Excellent Predictor of the Occurrence of Opportunistic Infections for HIV/AIDS



WARNING

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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Antiretroviral Therapy

When to Start ART Following Opportunistic Infection

When to Start ART Following Opportunistic Infection

- Most OIs
  - –Within 2 weeks of diagnosis

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When to Start ART Following Opportunistic Infection

- **Tuberculosis : 2-8 weeks**
  - CD4<50-within 2 weeks of diagnosis
  - CD4>50-within 8-~~12~~ weeks of diagnosis
- **Cryptococcal Meningitis:4-6 weeks after start of Ampho**
  - Sooner if mild and if CD4<50
  - Later (up to 10 weeks) if severe (CSF sterility reduces risk of IRIS)
- **"Untreatable" OIs, ie PML, Cryptosporidiosis**
  - Start immediately

Primary and Secondary OI Prophylaxis

- **Primary Prophylaxis**
  - PCP (CD4 <200, ~~oral candida, prior AIDS Defining~~)
  - Toxo (CD4 <100, positive anti Toxo IgG)
  - Cocci (CD4<250, 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

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*

*"Adequate response of primary disease"-see guidelines for details

Primary Coccidiomycosis Prophylaxis 2020 OI Guideline

Testing

- **Once or twice yearly testing for seronegative patients**
- **No prophylaxis if seronegative**

Primary Prophylaxis

- **Within the endemic area**
  - New positive IgM or IgG serology
  - CD4 count is <250 cells (BIII)
  - No Active Disease
- **Regimen**
  - Fluconazole 400mg qd until CD4>250 and fully suppressed viral load

www.aidsinfo.nih.gov

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

Recommendations May Vary from the Advisory Committee on Immunization Practices

VACCINE	All persons	Where varies by age				Where varies by CD4 cell count (cells/mm³)	
		13-26 years	27-49 years	50-64 years	≥ 65 years	< 200	≥ 200
Hepatitis A	2-3 doses (varies by formulation)						
Hepatitis B	2-3 doses (varies by formulation)						
Human papillomavirus (HPV)		3 doses	3 doses				
Influenza	1 dose annually						
Measles, mumps, rubella (MMR)						Contraindicated	2 doses if born after 1956 or nonimmune
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years						
Meningococcal B (MenB)	2-3 doses (varies by formulation)						
Pneumococcal conjugate (PCV13)	1 dose						
Pneumococcal polysaccharide (PPSV23)		2 doses five years apart			1 dose		
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once then Td or Tdap booster every 10 years						
Varicella (VAR)						Contraindicated	2 doses
Zoster recombinant (RZV) (preferred)				2 doses			

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

HBV Recommendation

- **Who to vaccinate**
  - All HIV+ who are HBs Ab negative
- **What Vaccine to Use**
  - Consider HAV/HBV combination (3-4 doses) (0,1,6 months +/1 2 month)
  - Either of the two recombinant vaccines is recommended-3 doses
  - **Adjuvant vaccine (Heplisav)** is more immunogenic but no firm recommendation for use in HIV-2 doses (months 0,1)
    - (Is Adjuvant associated with more cardiovascular events?)
- **Assure that serum ab level remains >10 IU/ml for patients with HIV**
  - Assess Ab 1-2 month after series completed and then annually
  - Booster for those still at risk if antibody <10IU

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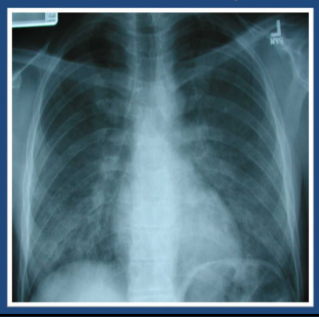
HBV Vaccination for HIV Infected Persons
Special Problems That Are Likely Untestable

- **What to do about Isolated HBc pos (HBs neg)**
  - Not testable
  - Give one dose: if titer rises to >100 IU, stop; if not >100 IU, complete 4 dose series
- **Initial Regimen Failures (Titers <10 IU)**
  - Give one booster
  - Give another 3 dose series
  - Give double dose 3-4 like dialysis patients
  - Give adjuvant vaccine
  - Wait for CD4 to rise due to ART

What Should You Know About "Newer" Vaccines?

- **Heplisav-B**
  - Hepatitis B vaccine, recombinant, adjuvanted (Dynavax)
  - Likely safe to use in HIV infected persons
  - Insufficient data in HIV for most guidelines to recommend as preferred
- **Shingrix**
  - Recombinant Vaccine with adjuvant (A501B)
    - Preferred over Zostavax (zoster vaccine live) for non HIV infected persons over 50 years
  - Split Decision for PLWH Recommendation
    - Insufficient data for ACIP guideline recommendation for HIV infected persons
    - "Preferred" in IDSA/CDC/NIH HIV guideline

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**
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  - **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)

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Approach to Diagnosis and Therapy of Pneumonia in Patients with HIV Infection

Parameter	Example
Rapidity of onset	> 3 days: PCP, TB <3 days: bacteria
Temperature	Afebrile: neoplasm
Character of sputum	Purulent: bacteria Scant: PCP, TB, virus
Physical Exam	Normal in PCP; Consolidation in Bacterial
X-ray	Pattern: Suggestive, but not definite

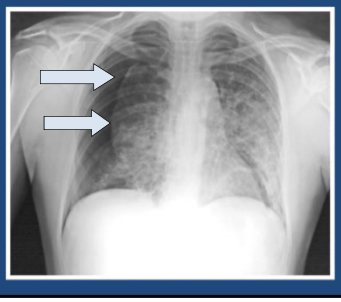
Pneumococcal Disease in Persons with HIV Infection

- CD4<200
  - 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

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

Pneumocystis Jirovecii (Formerly *P. carinii*)

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

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Host Susceptibility to PCP

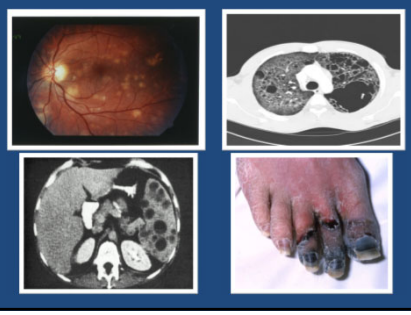
- CD4 < 200 cells/μL --(90% of cases)
- CD4% <14

Clinical Features of Pneumocystis Pneumonia, (n=168)

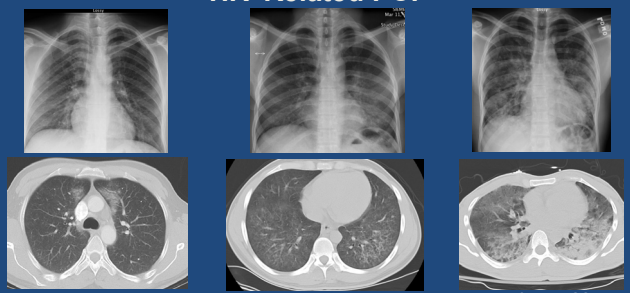
Symptom	% of Patients
Dyspnea	91%
Fever	66%
Cough	47%
Productive	7%
Non-productive	40%
Chest Pain	7%
Signs	
Cyanosis	39%
Rales	33%

Walzer, Ann Intern Med 1974

Uncommon Manifestations of PCP



HIV Related PCP



Asymptomatic
Incidental Finding

Fever, Wt. Loss, No SOB
Pulse Ox. 99%, to 89% w/Exercise

2 Weeks of Fever, SOB Room
Air PAO_2=67 mm Hg

Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

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

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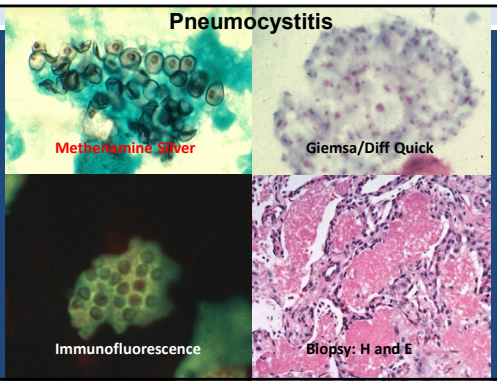
Radiologic Patterns Associated with Documented Pneumocystis Pneumonia

- **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
	1957	
Open lung biopsy		Methenamine silver
Transbronchial biopsy		Immunofluorescence
Bronchoalveolar lavage		Giemsa / Diff Quik
Induced sputum		PCR
	2020	

Pneumocystitis



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
- **Beta Glucan**
  - Sensitive but not specific
  - Maybe useful for
    - Heightened suspcicion of PCP if BAL or sputum not feasible
    - Following response to Rx

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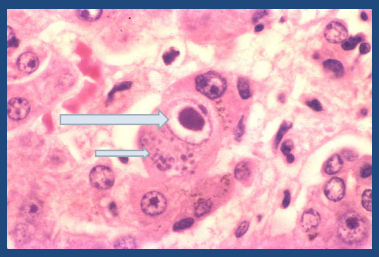
Question #4

- **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

Question #5

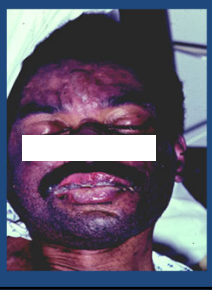
A 23 year old male with HIV Related PCP (CD4=25 cells/uL) was started on IV trimethoprim-sulfamethoxazole for PCP.

He is on no other meds

On day 7 of therapy, he developed fever, myalgias and on day 8 bullous skin lesions diffusely, most notably on his face, and developed substantial mucositis and a new fever to 39 C with pain over the blistered areas. His palms and soles were spared

Which of the following would be the most effective intervention:

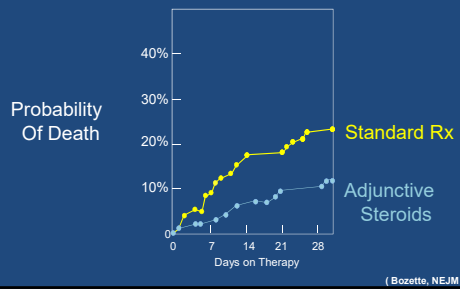
1) Add IV Acyclovir and swab lesions for HSV PCR
2) Add vancomycin for scalded skin syndrome
3) Switch TMP-SMX to IV Clindamycin plus oral Primaquine
4) Add IV Clindamycin to IV TMP-SMX
5) Add Prednisone to IV TMP-SMX



Therapy for Pneumocystis Pneumonia

- **Specific Therapy**
  - **First Choice**
    - **Trimethoprim-Sulfamethoxazole**
  - **Alternatives**
    - **Parenteral Pentamidine**
    - **Atovaquone**
    - **Clindamycin-Primaquine**
- **Adjunctive Corticosteroid Therapy**

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

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

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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

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

Question #6

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, and ABG which shows pH 7.40, pO2=96mmHg, pCO2 =39mm Hg, O2 Sat 79%.

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 #7

A patient with HIV infection presents with PCP (room air pO_2=84mHg).

He has a history of a severe exfoliative rash to TMP-SMX.

Which of the following therapies would you recommend:

A. **TMP-SMX plus prednisone**
B. **Dapsone plus trimethoprim**
C. **Aerosolized pentamidine**
D. **Intravenous pentamidine**
E. **Clindamycin-pyrimethamine**

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

Question-Non ARS

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.

What is this rhythm?

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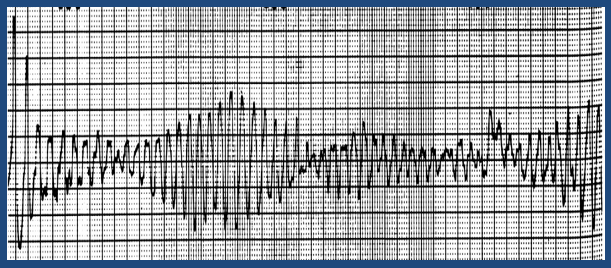
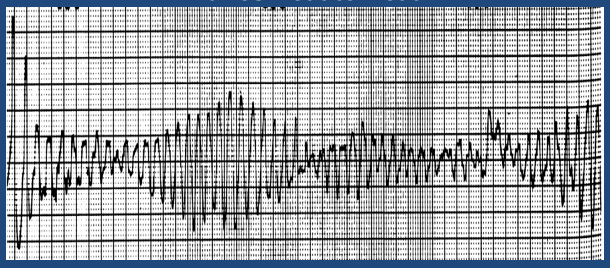
What is this rhythm?

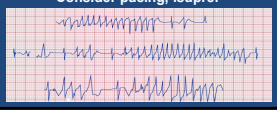


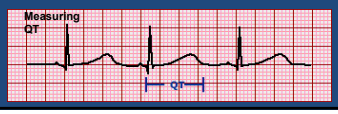
Polymorphic Ventricular Tachycardia Varies Beat to Beat



Prolonged QT

- **Prolonged QT predisposes to Torsades**
  - **Worry: >0.5 sec (500ms)**
  - **Corrected QT interval (QTc) is calculated by formula**
- **Therapy for Torsades**
  - **Fix underlying cause, stop offending drug(s)**
  - **If Pulseless: Defibrillate, epinephrine bolus, Magnesium**
    - **Magnesium sulfate 2g bolus**
    - **Consider pacing, isuprel**





Causes of Prolonged QT

Electrolytes

Hypo: magnesemia, kalemia, calcemia

Antibiotics

- Pentamidine
- Chloroquine/Hydroxychlor
- Clarithromycin
- Atazanavir
- Quinolones
- Quinidine
- Azoles

Other Drugs

- Tricyclic antidepressants
- Disopyramide (Norpace)
- Amiodarone
- Sotalol
- Thioridazine
- Procainamide
- Haloperidol

Question #8

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

Toxicities of TMP-SMX and Pyrimethamine-Sulfadiazine

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

13 – Management of AIDS-Related Opportunistic Infections I

Speaker: Henry Masur, MD

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	Absorption if low fat diet Rash, N + V, diarrhea, LFT

Other Conditions Where PCP Is Common

- **Prednisone >=20mg qd x > 4 weeks**
- **Cytoxan**
- **Purine Analogs**
  - Azathioprine - Mercaptopurine
  - Pentostatin -Fludarabine
- **Various Biologics**
  - Rituximab
  - Alemtuzumab (Campath) for at least 2 months post therapy or until CD4>200
  - TNF Inhibitors
  - Acute lymphocytic leukemia during acute and maintenance therapy
  - Allogeneic stem cell transplant recipients, at least 6 months
  - Graft vs host disease
  - Solid organ transplant recipients, at least 6 months and during acute rejection rx
  - Idelalisib, a phosphatidylinositol 3-kinase inhibitor
  - Probably: Ibrutinab, TNF Inhibitors
  - Concomitant temozolomide and radiotherapy, until recovery of lymphopenia

Thank You!