

HIV Opportunistic Infection Update

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Case

- **A 47 year old woman with AIDS (CD4 37, V.L. 90,000) presents to your clinic with fever of 103 daily for 4 weeks. She has had watery diarrhea for 6 weeks. Physical exam shows muscle wasting and splenomegaly. A CXR is normal.**
 - **What is the differential diagnosis?**
 - **What should you do now?**

HIV/AIDS Fever Differential Diagnosis

- **M. avium Bacteremia**
- **Miliary Tuberculosis**
- **Disseminated Pneumocystis**
- **Cryptococcosis**
- **Disseminated Coccidioidomycosis**
- **Bacillary Angiomatosis**
- **CMV**
- **Non-Hodgkin's Lymphoma**

Fever Physical Exam

- Adenopathy may suggest MAC or TB
- Retinal lesions may suggest CMV
- Umbilicated skin lesions suggest cryptococcosis
- Purple-red raised nodules suggest bacillary angiomatosis

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Initial Fever Evaluation

- **CMP, CBC, CXR, Blood Cultures**
- **Bactec Blood Culture**
- **PPD skin test**
- **Lumbar Puncture**
- **Sputum induction for PCP and AFB**
- **Dilated fundoscopic exam**

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Fever Evaluation continued

- **Abdominal CT**
- **Bone Marrow**
- **Consider:**
 - **Liver biopsy**
 - **Skin biopsy**
 - **Endoscopy**

M. avium Review

- Slow growing Acid-Fast Bacillus seen when CD4 <50
- Patients present with fever, sweats and chronic diarrhea.
- Cachexia, hepatosplenomegaly and lymphadenopathy are often seen on physical exam.
- Pancytopenia and elevated alkaline phosphatase are

MAC Diagnostics

- Bactec Blood cultures are the test of choice.
 - Positive in 7-10 days
- Other cultures helpful but invasive:
 - Bone Marrow : Positive in 17 of 30 blood culture positive cases
 - Gut biopsy useful to document mucosal invasion
- Sputum and stool Cx are not reliable.
- CT Abdomen : Adenopathy seen in 42% of cases

MAC Therapeutics

- Basic Therapy
 - Clarithromycin 500 mg po BID
 - Plus
 - Ethambutol 15-20 mg/kg po QD

MAC Therapeutics

- Treatment Options:
 - Addition of Rifabutin 300 to 450 mg po QD is optional if > 100 organisms per ml or HAART ineffective.
 - Azithromycin: if GI intolerance or drug interactions
 - Treat until CD4 > 200 for 6 months and cultures negative for 12 months

MAC Therapeutics

- Salvage Regimen
 - Amikacin 10 mg/kg iv QD
 - *plus either*
 - Ciprofloxacin 500 mg po BID
 - *or*
 - Rifabutin 300-450 mg po QD

MAC Prevention

- Start Azithromycin 1200 mg po weekly if CD4 < 50
- Stop Prophylaxis if CD4 > 100 for 3 months

HIV/AIDS Update

Case

- A 27 year old male with a history of IDU now notes 5 days of non-productive cough. He has lost 3 pounds since the last visit. Physical exam is notable for cachexia. When he walks around the clinic his oxygen saturation drops to 84%.
 - What is the differential diagnosis?
 - What should you do now?

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Pulmonary Infiltrate Differential

- Bacterial pneumonia
- Tuberculosis
- M kansasii
- Pneumocystis
- Toxoplasmosis
- Cryptococcosis
- Coccidioidomycosis
- Blastomycosis
- Aspergillosis
- Strongyloidiasis
- CMV
- VZV
- Kaposi's Sarcoma
- Lymphoma
- Lymphocytic Interstitial Pneumonitis

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Initial evaluation of infiltrates

- Routine Gram stain and culture
- Blood cultures
- Sputum AFB smear and culture X 3
- Induced sputum for PCP immunofluorescence

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Pulmonary Infiltrate Therapy

- Typical pneumonia, CD4 > 500
 - -Third generation cephalosporin plus a macrolide
- Atypical pneumonia, CD4 < 500
 - Trimethoprim/Sulfa plus a cephalosporin plus a macrolide

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Further Infiltrate evaluation

- What to do next if routine tests are negative
 - Bronchoalveolar Lavage
 - Transbronchial lung biopsy
 - Transcutaneous lung biopsy

PCP Pneumonia

- *Pneumocystis jiroveci* is the causative agent
- Still called “PCP”
- Classified now as a fungus
 - Cell wall has Beta-D-glucan
 - Ubiquitous in the environment
 - Can be transmitted from one immunocompromised host to another.

PCP Clinical Presentation

- Typical symptoms
 - Nonproductive Cough (95%)
 - Fever (79-100%)
 - Dyspnea (95%)
- Extrapulmonary disease (pentamidine nebs)
 - Liver
 - Spleen
 - Kidney
 - Brain

PCP Radiology

- CXR:
 - Bilateral diffuse interstitial and alveolar infiltrates
 - Small Cysts
 - Effusions
 - Pneumothorax
- CT Scan:
 - Ground glass infiltrate have 100% sensitivity, 89% specificity

PCP Diagnostics

- Induced sputum
 - GMS
 - Geimsa
 - PCP Immunofluorescence
- Bronchoscopy
 - BAL
 - Transbronchial Biopsy

Other PCP diagnostics

- Beta-D Glucan Assay (Watanabe, Clin Infect Dis 2009):
 - 96% sensitivity
 - 88% specificity
- S-adenosylmethionine assay
 - Required for growth of PCP
 - Levels are depleted in patients with PCP
 - Requires HPLC device

PCP Treatment (21 days)

- Parenteral Regimens

- Trimethoprim-Sulfa: 5 mg/kg IV q 8h for 21 days
- Pentamidine 4 mg/kg IV daily for 21 days

- Oral Regimens

- Tmp/SMZ DS 2 po tid
- TMP 5 mg/kg po tid plus Dapsone 100 mg po qday
- Clinda 450 mg po qid plus Primaquine 15 mg po qday
- Atovaquone 750 mg po bid

PCP Adjunctive Rx

- Give Steroids if
 - A-a gradient \geq 35mm or
 - pAO₂ \leq 70mm
- Prednisone
 - 40 mg po bid for 5 days then
 - 40 mg po daily for 5 days then
 - 20 mg po daily for 21 days

PCP Prophylaxis

- TMP/SMZ DS 1 po daily or TIW
 - Dapsone 100 mg po daily
 - Atovaquone 750 mg po bid
 - Pentamidine neb 300 mg monthly
-
- Stop when CD4 count is > 200 for 3 months

HIV/AIDS Update

Case

- A 53 year old woman with HIV now has diarrhea. She was treated with ZDV/3TC/NFV originally but now is on a second regimen including TDF/FTC/ATZ/rbv. She notes 6 weeks of watery stools without fever or blood
 - What is the differential diagnosis?
 - What should you do now?

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Diarrhea

- **Chronic**

- CMV
- Microsporidia
- Cryptosporidia
- MAC
- Isospora
- Cyclospora
- Giardia

- **Acute**

- Shigella
- Salmonella
- Campylobacter
- C. Difficile

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Diarrhea

- **Bloody**

- Shigella
- Salmonella
- Campylobacter
- C. difficile
- CMV
- Entamoeba

- **Watery**

- Microsporidia
- Cryptosporidia
- MAC
- Isospora
- Giardia
- Entamoeba
- Cyclospora

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Diarrhea work up

- Initial evaluation
 - CBC, electrolytes, BUN, Creatinine, LFTS
 - Routine stool culture
 - Clostridium difficile toxin assay
 - Stool Ova and Parasites exam
 - Stool Trichrome stain
 - Stool Modified AFB Stain

NAIHS HIV/AIDS Diarrhea workup

- Further workup
 - Upper endoscopy with small bowel Bx.
 - Colonoscopy with Bx.

Microsporidiosis

- Spore forming protozoan with fungal characteristics
- Ubiquitous in the environment
- 1-2 microns in size
- Two species
 - *Enterocytozoan bieuneusi*- major cause of diarrhea
 - *Encephalitozoan cuniculi and hellem*- disseminate
- Distort small bowel villous architecture

Microsporidiosis

- Clinical syndrome:
 - Profuse watery diarrhea
 - Median CD4 is 20
 - Biliary, lung, corneal, renal disease and encephalitis all occur
- Diagnosis
 - Modified trichrome stain

Microsporidiosis

- Treatment
 - Albendazole 400 mg po bid for *Encephalocytozoan sp*
 - No reliable Rx for *Enterocytozoan bienusi*

Cytomegalovirus colitis

- CMV is a herpesvirus that infects latently
- AIDS patients affected when CD4 <50
- CMV viremia is a risk factor for subsequent invasion

Cytomegalovirus

- Clinical Manifestations
 - Esophagitis with odynophagia, fever and nausea
 - Gastritis with epigastric pain but rarely bleeds
 - Enteritis of small bowel: pain and diarrhea
 - Colitis: fever, weight loss, watery diarrhea and hemorrhage

Cytomegalovirus colitis

- Diagnosis:
 - PCR of blood
 - Biopsy: cytomegalic cells with eosinophilic intranuclear and basophilic cytoplasmic inclusions.

CMV Treatment

- Gancyclovir induction 5 mg/kg IV q 12 hrs then Valgancyclovir 900 mg po bid when better for 3-6 weeks
- Maintenance therapy with daily VGC for relapsed cases
- Support WBC with G-CSF
- Foscarnet is usually reserved for salvage therapy

Case presentation

- A 51 year old man with HIV develops sudden visual impairment in the right eye. He has had low grade fevers for a few weeks. His last CD4 count was 97 and the viral load is $> 100,000$.

CMV Retinitis

- Affect 47% of patients with CD4 < 50
- If no HAART is given, median time to progression is 47-104 days.
- Median time to death was 0.65 years in the pre HAART era.

CMV Retinitis

- Symptoms:
 - Scotomata
 - Floaters
 - Photopsia “flashing lights”

CMV Retinitis

- Examination
 - Fluffy lesions near vessels with hemorrhage
 - Fulminant (hemorrhagic)
 - Indolent (non hemorrhagic)
 - Mixed
 - Retinal detachment
 - Immune Reconstitution uveitis
 - Vitreous involvement is pathognomonic for IRIS

CMV Retinitis Treatment

- First line:
 - Valganciclovir 900 mg po bid for 14-21 days then 900 mg po daily until CD4 >100 for 3-6 months
- If <1500 microns from fovea or near optic head
 - IV gancyclovir
 - Gancyclovir ocular implant or injection
- Other drugs
 - Foscarnet
 - Cidofovir

CMV Immune reconstitution uveitis

- Manifestations
 - Vitritis
 - Cystoid Macular edema
 - Epiretinal membranes
- Treatment
 - Steroids controversial
 - Valganciclovir

HIV/AIDS Update Case

- A 45 year old man with AIDS (CD4 85) now has a headache of three weeks duration. His friends say he is confused. Your neurologic exam reveals a left pronator drift.
 - What is the differential diagnosis?
 - What should you do now?

Differential for paralysis in AIDS

- **Brain**

- Toxoplasmosis
- Lymphoma
- TB
- Cryptococcosis
- Nocardia
- Brain abscess
- PML

- **Upper motor neuron**

- Vacuolar myelopathy
- TB
- Lymphoma
- Epidural abscess

- **Lower Motor Neuron**

- CIDP
- Mononeuritis multiplex
- CMV polyradiculopathy

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Evaluation for paralysis in AIDS

- **Initial work-up**
 - Head CT scan
 - Lumbar Puncture

- **Further work-up**
 - MRI of brain or spine for upper motor neuron Dz
 - NCV/EMG for lower motor neuron Dz

Brain Mass Lesion

- Three major clinical entities
 - Toxoplasmosis:
 - More often multiple
 - Primary CNS Lymphoma (PCNSL)
 - Half the time solitary
 - If $\geq 4\text{cm}$, PCNSL is more likely
 - Progressive Multifocal Leukoencephalopathy
 - Usually non-enhancing
 - Will enhance if IRIS is present after institution of ART

Brain Mass Lesion Evaluation

- If no mass effect, proceed with LP and treat
 - Toxo (+) → toxoplasmosis
 - EBV (+) → CNS lymphoma
 - JC virus (+) → PML
- If mass effect and herniating, proceed with brain biopsy
- If mass effect and not herniating and Toxo Ab positive → a trial of anti toxo Rx

Toxoplasmosis

- Caused by *Toxoplasma gondi* a protozoan
- Causes latent infection, reactivates when CD4 < 100
- Acquired through exposure to cats and eating poorly cooked meats

Toxoplasmosis

Clinical manifestations

- Encephalitis:
 - headache, confusion, fever, dull affect
- Pneumonia
 - Fever and dry cough
 - Reticulonodular infiltrate
- Chorioretinitis
 - Yellow, cotton-like infiltrates

Toxoplasmosis

- Diagnosis

- Serology
- CT or MRI with contrast
- SPECT or PET: (decreased thallium uptake and glucose use with toxo)
- Biopsy: 3-4% morbidity rate
- PCR: 50-98% sensitive, 96-100% specific

Toxoplasmosis

- Treatment
 - Pyramethamine 200 mg po x1 then 50-75 mg po daily
 - Sulfadiazine 1-1.5 gm po qid
 - Leukovorin 10-25 mg po daily
 - Clindamycin is substituted for sulfadiazine if sulfa allergic

Three more paralysis syndromes

- Vacuolar myelopathy: Upper motor neuron
 - spastic
 - hyper-reflexic
 - no pleocytosis
 - normal glucose

Three more paralysis syndromes

- Chronic Inflammatory Demyelinating Polyneuropathy
 - Looks like Guillain Barre Syndrome
 - Flaccid
 - Areflexic
 - High CSF protein is the hallmark
 - Pretty good prognosis with treatment

Three more paralysis syndromes, contd

- **CMV Polyradiculopathy**

- Flaccid
- Areflexic
- Polys in CSF suggesting bacterial meningitis
- Low glucose suggesting bacterial meningitis

- **CMV Ventriculoencephalitis**

- Polys in CSF and low glucose
- Periventricular enhancement

Three more paralysis syndromes

- Treatment

- Vacuolar Myelopathy: ART

- CIDP: ART plus steroids and plasmapheresis

- CMV Polyradiculopathy: ganciclovir +/- foscarnet