HIV Opportunistic Infection Update

Jonathan Vilasier Iralu, MD, FACP
Indian Health Service  Chief Clinical Consultant for Infectious Diseases
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
NAIHS HIV/AIDS
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
• 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
• 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?
NAIHS HIV/AIDS
Pulmonary Infiltrate Differential

- Bacterial pneumonia
- Tuberculosis
- M kansasii
- Pneumocystis
- Toxoplasmosis
- Cryptococcosis
- Coccidioidomycosis
- Blastomycosis
- Aspergillosis

- Strongyloidiasis
- CMV
- VZV
- Kaposi’s Sarcoma
- Lymphoma
- Lymphocytic Interstitial Pneumonitis
NAIHS HIV/AIDS
Initial evaluation of infiltrates

• Routine Gram stain and culture
• Blood cultures
• Sputum AFB smear and culture X 3
• Induced sputum for PCP immunofluorescence
NAIHS HIV/AIDS
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
NAIHS HIV/AIDS
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 ≥ 35mm or
  – pAO2 ≤ 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/rtv. She notes 6 weeks of watery stools without fever or blood
  – What is the differential diagnosis?
  – What should you do now?
NAIHS HIV/AIDS
Diarrhea

• **Chronic**
  – CMV
  – Microsporidia
  – Cryptosporidia
  – MAC
  – Isospora
  – Cyclospora
  – Giardia

• **Acute**
  – Shigella
  – Salmonella
  – Campylobacter
  – C. Difficile
NAIHS HIV/AIDS
Diarrhea

• **Bloody**
  – Shigella
  – Salmonella
  – Campylobacter
  – C. difficile
  – CMV
  – Entamoeba

• **Watery**
  – Microsporidia
  – Cryptosporidia
  – MAC
  – Isospora
  – Giardia
  – Entamoeba
  – Cyclospora
NAIHS HIV/AIDS
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
  - *Encephalitozoon 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
NAIHS HIV/AIDS
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 $\geq 4$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 +)\(\rightarrow\) toxoplasmosis
  – EBV (+)\(\rightarrow\) CNS lymphoma
  – JC virus (+)\(\rightarrow\) PML

• If mass effect and herniating, proceed with brain biopsy

• If mass effect and not herniating and Toxo Ab positive\(\rightarrow\) 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 sulfdiazine 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