Recognition and Diagnosis of AIDS-Related Opportunistic Infections

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Learning Objectives

Upon completion of this presentation, learners should be able to:

• Match risk of opportunistic infections (OI’s) with immune status of HIV+ clients in their practice.
• Recognize symptoms of the most common and important OI’s in their HIV+ clients.
• Select which diagnostic tests to order for HIV+ clients presenting with symptoms of a common OI.
Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Case # 1:
A Guy Walks into your ED…

CC: fever, headache, cough, weight loss
    : 34 year old patient is HIV-positive “for
    years” and is not on any medicines

PMHx:
    Ex-smoker, moderate alcohol (none lately)
    Was homeless for 6 months in past year
    No history of other illnesses

Physical exam: T 100.4, BP and rest normal
Case # 1: Multiple Symptoms

• The most likely diagnosis in this patient is:
  – A) *Pneumocystis jirovecii* (PCP) pneumonia
  – B) *Mycobacterium avium* infection (MAC)
  – C) CMV infection
  – D) Cryptococcal meningitis
  – E) Can’t tell – not enough information
  – F) A, B, C & D – could be anything with HIV
Case # 1: Answers

• Correct answer – E (not enough info)
• Fever is a very common sign of AIDS OI’s
• Important adjunct to work-up – CD4 count

• **Risk of OI’s tied to loss of CD4’s:**
  – CD4 < 200 – increased risk for PCP
  – CD4 < 100 – increased risk for toxoplasma
  – CD4 < 50 – ↑ risk for CMV, MAC, lymphoma
Natural history of untreated HIV infection and relationship of specific opportunistic infections to CD4 count.

Wilcox C M, Saag M S Gut 2008;57:861-870
AIDS-Related OI’s: Overview

• Several studies as well as clinical experience provide data to help sort through possibilities.

• Will review:
  – Candida esophagitis
  – CMV retinitis
  – Cryptococcal meningitis
  – Cryptosporidium, microsporidium
  – *Mycobacterium avium* complex infection
  – *Pneumocystis jirovecii* pneumonia (PCP)
  – Progressive Multifocal Leucoencephalopathy (PML)
  – Toxoplasmic brain abscess
Case # 2: 
More about that guy in your ED…

• CC: fever, mild HA and cough x 3 weeks

• Further history:
  – fever up to 102, little appetite, no nausea or vomiting
  – Coughing (dry) for weeks; now SOB with talking
  – Homeless x 6 mo/past year, ex-smoker, some alcohol

• Exam: thrush, clear lungs, rest normal

• Labs are pending; \( pO_2 = 70 \text{ mm Hg} \)

• CXR: slight increase in bronchial markings
Which of the following is **TRUE** about this patient?

1. Need a CD4 cell count before going further.
2. Differential diagnosis includes bacterial pneumonia, TB and pneumocystis.
3. This patient will likely require a bronchoscopy for definitive diagnosis
4. Work-up should include a spiral CT to rule out pulmonary embolus
5. 2 and 3
6. All the above
Case # 2: Answers

• Correct answer – 5 (2 and 3 only).
• Presence of thrush = risk for PCP
• Also at risk for CAP and TB –
  – empiric Rx = at least 7 drugs
  – If add steroids, lose fever as monitoring sx
• BAL recommended for accurate diagnosis.
• Symptoms not typical for PE – PCP comes on slowly over days to weeks
When to Suspect PCP

• CD4 count < 200 (or CD4% < 14) + symptoms
• Thrush or oral hairy leukoplakia
• Hypoxemia with normal CXR
• CXR –
  – diffuse bilat symmetrical interstitial infiltrates
  – pneumothorax with AIDS (think PCP)
  – cavitation, adenopathy and effusions **not** common
• Non-specific:
  – Increased LDH > 500, O₂ desat with exercise
With CD4<200 and no HIV meds, no prophylaxis - 70-80% will develop PCP
Diagnosis of PCP

• Presumptive – with classic presentation
  – response to empiric therapy for PCP
  – thin-slice CT – patchy ground-glass attenuation
  – gallium scan – diffuse uptake both lungs

• Definitive:
  – Histologic confirmation on induced sputum or BAL samples
  – variety of stains available; nucleic acid tests
Gomori methenamine silver stain

Courtesy of CDC, Dr. Russell Brynes
Direct Immunofluorescence Staining

Courtesy of CDC, Lois Norman
Diagnosis of PCP - 2

Sensitivity of stained respiratory secretions

<table>
<thead>
<tr>
<th>Source</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced sputum</td>
<td>&lt; 50% - 90%</td>
</tr>
<tr>
<td><strong>BAL</strong></td>
<td>90 – 99%</td>
</tr>
<tr>
<td>Trans-bronchial Bx</td>
<td>95 – 100%</td>
</tr>
<tr>
<td>Open lung bx</td>
<td>95 - 100%</td>
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</tbody>
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Early BAL allows focused therapy (1-2 drugs instead of 7), ID of co-infection(s), & earlier release from isolation.
Case # 3: A 33-y/o Woman Walks into Your Clinic as a New Patient

CC: mid-sternal chest pain and odynophagia

Hx: HIV +, took meds when pregnant, none for 8 yrs

Exam: nl except P 110 and thrush

EGD shown

Courtesy of CDC
Which of the Following is True?

1. This woman probably ignored the warning sign of a painful mouth indicating thrush.
2. You will be sued for malpractice if you did not get an EGD.
3. Fluconazole is sufficient treatment as most cases are caused by *C. albicans*.
4. This will respond to H2-blockers/ PPI’s.
5. If in care, this patient would have been on prophylaxis.
Case # 3: Candida esophagitis

• Correct answer: 3 (fluconazole)
• Thrush is commonly asymptomatic.
• EGD - required for definitive dx; many treat empirically and save this for failures.
• C. albicans most common; other species (C. glabrata) with advanced disease.
• With thrush and odynophagia, more appropriate treatment is for candida.
• No prophylaxis available.
Candida esophagitis

- CD4’s usually < 200
- Differential diagnosis:
  - Viral esophagitis:
    - CMV (CD4’s usually < 50), HSV
    - Aphthous ulcers
  - Barrett’s, severe GERD
- Culture thrush or esophagitis only if suspect resistance (treatment failure)
Case # 4: Confusion in an HIV Patient

• 36 y/o man, lethargic & confused
• Previous admission for PCP pneumonia 2006; history of injecting heroin.
• Exam:
  – BP 150/88, T 100.9, P 100, O2 sat 100% RA
  – No localizing signs, no rash
  – Fundoscopic exam – discs sharp
• Initial labs – hct 28, WBC 8000, Na 132
Case # 4: Which of the following statements is FALSE?

1. Unless on HIV treatment, patient’s CD4 count very likely < 200
2. Diff dx: includes brain abscess, meningitis and West Nile infection.
3. This patient needs CT or MRI before LP.
4. Non-focal, and urgently need data, so do the LP before imaging.
5. E. Bacterial endocarditis is also possible.
Case # 4: AIDS and Confusion

- Correct answer: 4 (non-focal, do LP)
- Patients with advanced HIV have cerebral atrophy so may lack signs of increased intra-cranial pressure.
- CT or MR scanning required to determine presence of space-occupying lesions.
- Expect very low CD4’s
  - total WBC also low - best to interpret WBC’s in light of past tests.
Patient Gets a CT Scan
CNS Focal Defects in AIDS

**Differential diagnosis**: (* = most common if CD4 low)
- Toxoplastic encephalitis*
- TB
- PML (fever absent)
- Primary CNS lymphoma*
- Cryptococcal meningitis
- Bacterial abscess
- Chagas disease
- PML – insidious focal neurologic defects (no fever)

**Symptoms:**
- Headache and fever, focal encephalitis, confusion, motor weakness
- PML – insidious focal neurologic defects (no fever)
Dx: Toxoplastic encephalitis

- Ubiquitous protozoan; cat definitive host
- Seroprevalence ~15% in US
- Reactivation of latent infection –
  – inflammation and mass effect.
- **Serology – IgG antibodies most useful.**
- **Typical CT/MR findings: multiple enhancing lesions**
- Brain biopsy, histopathology definitive
Diagnosis of Brain Abscess in AIDS

- Patient HIV+, CD4’s < 100
- Double-contrast CT or MRI – typical lesions
- Empirically treat as toxo for 2-3 weeks – response?
  - Yes - presumptive diagnosis of toxo
  - No - do brain biopsy
- Consider early biopsy if –
  - solitary lesion, negative toxo serology
Diagnosis: Cryptococcus meningitis

- Initial AIDS dx in 10% if CD4’s < 200
- Symptoms: fever and headache +/- focal signs (classic meningeal signs in 25-35%)
- Diff Dx: bacterial, syphilis, other fungi, JCV
- CT negative (usually) for masses
- Dx: Cryptococcal antigen – blood, CSF
- CSF: ↓/nl sugar, ↑protein, + India Ink (70%), few cells
- Cultures
Diagnosis: PML

• First have to suspect it:
  – recognize steady progression of focal neurological deficits,

• No one pattern; depends upon brain area:
  – hemiparesis, hemisensory loss, dysmetria, ataxia, hemionopsia
  – seizures in 20%
  – fever and headache absent
More Diagnosis: PML

- MRI: usually confirms distinctive white matter lesions
  - hyperintense T2 images, hypointense on T1 – helps tell from HIV encephalitis
  - no mass effect
- CSF for JCV DNA (+ in 70-90% if not on ART)
- Consider also: VZV, lymphoma
- Brain biopsy: typical histology, confirm JC virus
PML in Patients on HAART

- Immune reconstitution on ART can precipitate an atypical PML (IRIS PML).

- Can see mass effect and sometimes contrast enhancement on imaging.

- Histology different: mononuclear perivascular inflammation

- JC virus may be harder to detect in CSF
CMV Disease in HIV

• Usually occurs when CD4’s < 50
  – frequently have had other OI’s
• 50-90% of normal adults CMV antibody (+)
• Disease manifests as:
  – Retinitis: before HAART, 30% developed this
  – GI: colitis (5-10%), esophagitis (<5-10%)
  – Pneumonitis (uncommon)
  – Neuro: encephalitis, polyradiculomyelopathy
CMV Retinitis

- Unilateral in 2/3 at first (if no Rx, becomes bilateral)
- Symptoms:
  - peripheral disease: may be asymptomatic; floaters, scotoma, peripheral field defects
  - central disease: ↓ vision, central field cuts
- Diagnosis:
  - Retinal exam by experienced ophthalmologist
  - CMV antibodies a waste of money
  - In other sites, need histopathology (not c/s)
Do You Recognize This?

(hint: AFB smear)
Disseminated MAC
Mycobacterium avium complex

• Think MAC in patients with CD4 < 50 &:
  – fever and weight loss, +/- diarrhea, +/- N/V
  – anemia, hepato-splenomegaly and ↑ Alk PO4
  – +/- mediastinal, intra-abdominal adenopathy ** (no adenopathy peripherally)

• Organism is ubiquitous –
  – portal of entry pulmonary or GI

• If no HAART or prophylaxis, 20-40% get MAC

• At risk: other OI’s, colonization with MAC, high HIV viral load
Disseminated MAC: Diagnosis

• **Cultures**
  – blood, lymph node, bone marrow
  – Species ID:
    • specific DNA probes, HPLC, or biochemical tests

• **Histopathology and special stains**
  – biopsy material – cannot tell from TB or other mycobacteria
AIDS and Chronic Diarrhea

• All of the following are more common as causes of chronic diarrhea in HIV infection EXCEPT:

1. *Isospora belli*
2. *Giardia lamblia*
3. Cryptosporidiosis
4. *Cyclospora*
5. Microsporidial species
AIDS and Chronic Diarrhea

• Answer: 2 – *Giardia lamblia*

• Other 4 are increased in HIV-infected persons

• Sexual activity of HIV+ persons may put them at increased risk for Giardiasis

• *Isospora* and *Cyclospora* rare in the US
Diarrhea: Differential Diagnosis

- **Viral**
  - Cytomegaloviral colitis
  - HIV enteropathy
  - KS of the bowel

- **Parasitic**
  - *Cryptosporidium*
  - *Isospora belli*
  - *Cyclospora*
  - *Microsporidial species*
  - Giardia lamblia
  - Entamoeba

- **Bacterial**
  - *Salmonella*
  - *Shigella*
  - *Yersinia*
  - *Campylobacter*
  - Mycobacterial
  - *Clostridium difficile*

- **Fungal**
  - Candidal overgrowth of the large bowel
Cryptosporidiosis

• Spore-forming protozoa
  – # 1 cause of protozoal diarrhea worldwide

• Intestinal infection
  – usually infects small bowel but also colon
  – profuse watery, large-volume stools, cramps
  – non-invasive: may infect gallbladder

• Infectious dose 10 oocysts

• Usually acute disease, chronic when CD4 < 180-200
Cryptosporidiosis: Diagnosis

- Only 4 micrometers in diameter
- Diagnosis by
  - modified acid-fast stain of stool for oocysts
  - Direct immunoflourescent assays
  - ELISA in stool or tissues
  - Small intestinal biopsy
  - 1 stool usually sufficient for diagnosis
Microsporidiosis

• Multiple genera & species
  – *Encephalitozoon cuniculi, hellem, intestinalis*, *Enterocytozoon bieneusi, Trachipleistophora hominis, anthropophthera, Pleistophora ssp.*

• Obligate intracellular protozoa

• 7-50% seroprevalence; can be asymptomatic

• Diseases: most common - diarrhea
  – keratoconjunctivitis, sinusitis/respiratory, hepatitis, encephalitis, cholangitis, myositis
Microsporidiosis: Diagnosis

- Three stools for stain with chromotrope 2R and/or chemofluorescent stains (1-4 mcm)
- Urine for spores (only 2 species)
- If above negative, small bowel biopsy – can be seen with a variety of stains
- Species determination requires electron microscopy
- Responds to Rx (cryptosporidiodsis not)
Summary: Recognition and Diagnosis of AIDS OI's

- CD4 cell count helps with differential diagnosis.
- Most OI’s organisms are either from environmental sources or latent infections.
- Without HIV meds or prophylaxis, most common OI’s are:
  - PCP, disseminated MAC and CMV retinitis
Summary - 2

• These OI’s require tissue and/or demonstration of organisms for diagnosis:
  – PCP, MAC, Cryptococcus, Cryptosporidium, microsporidium, CMV (non-retinitis)

• Diagnosed by examination: CMV retinitis

• (Initial) Diagnosis by empiric Rx:
  – toxoplasmic brain abscess and candida esophagitis

• Diagnosed by PCR or antigen testing: Cryptococcus, PML
References

• MMWR 2009 (April); 58: No RR-4
  – prevention & treatment of OI’s in adolescents & adults
• MMWR 2009 (Sept); 58: No RR-11
  – prevention & treatment of OI’s in infants, children
• AIDS Education and Training Centers’ National Resource Center
  – www.aidsetc.org
• For pictures, including x-rays, www.aids-images.ch
• NIH, CDC websites