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

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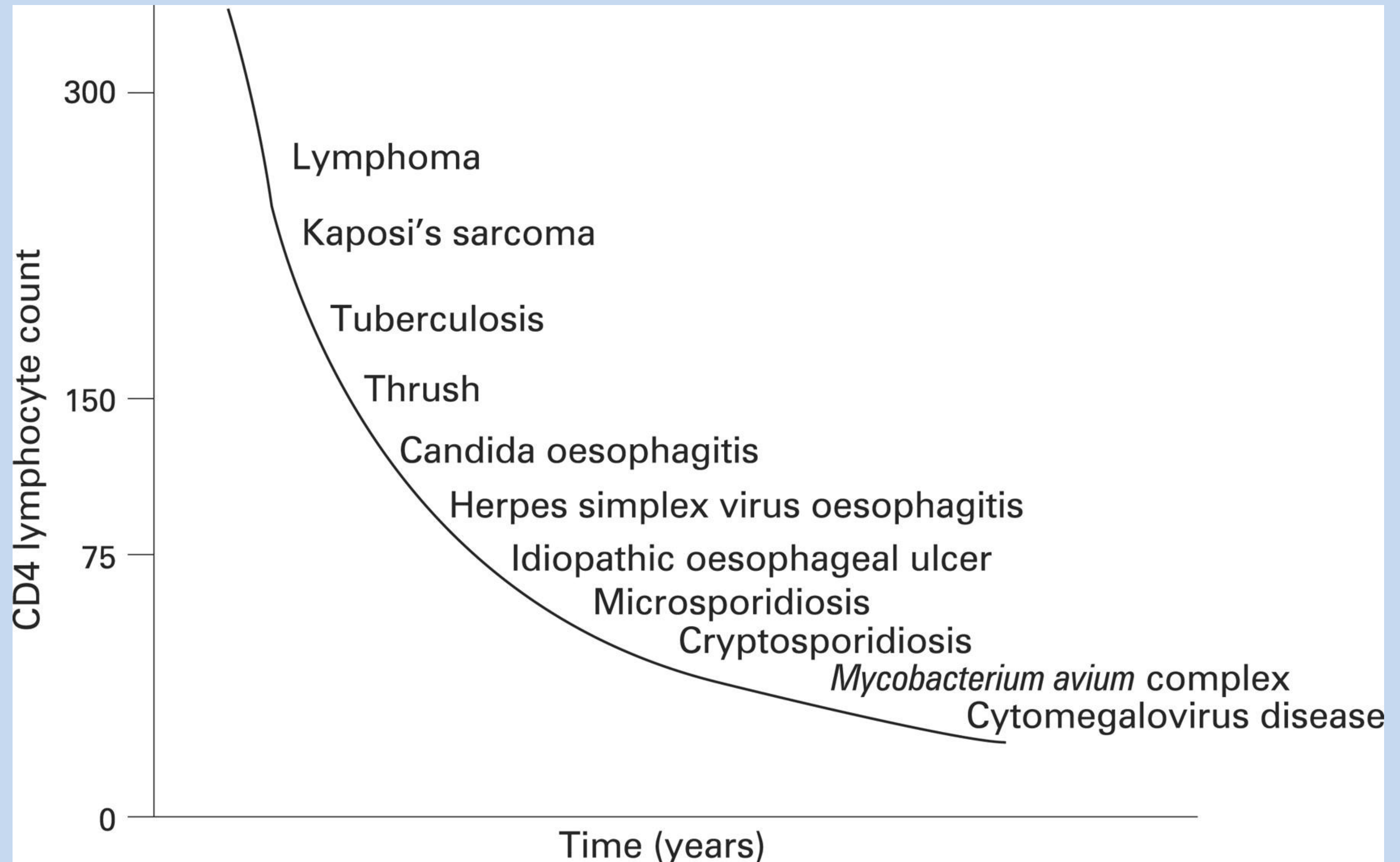
Case # 1: Answers

- 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

GUT

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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

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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 mm Hg
- CXR: slight increase in bronchial markings

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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

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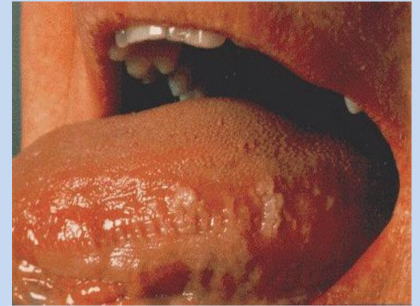
When to Suspect PCP

- 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 <u>not</u> common
- Non-specific:
  - Increased LDH > 500, O_2 desat with exercise



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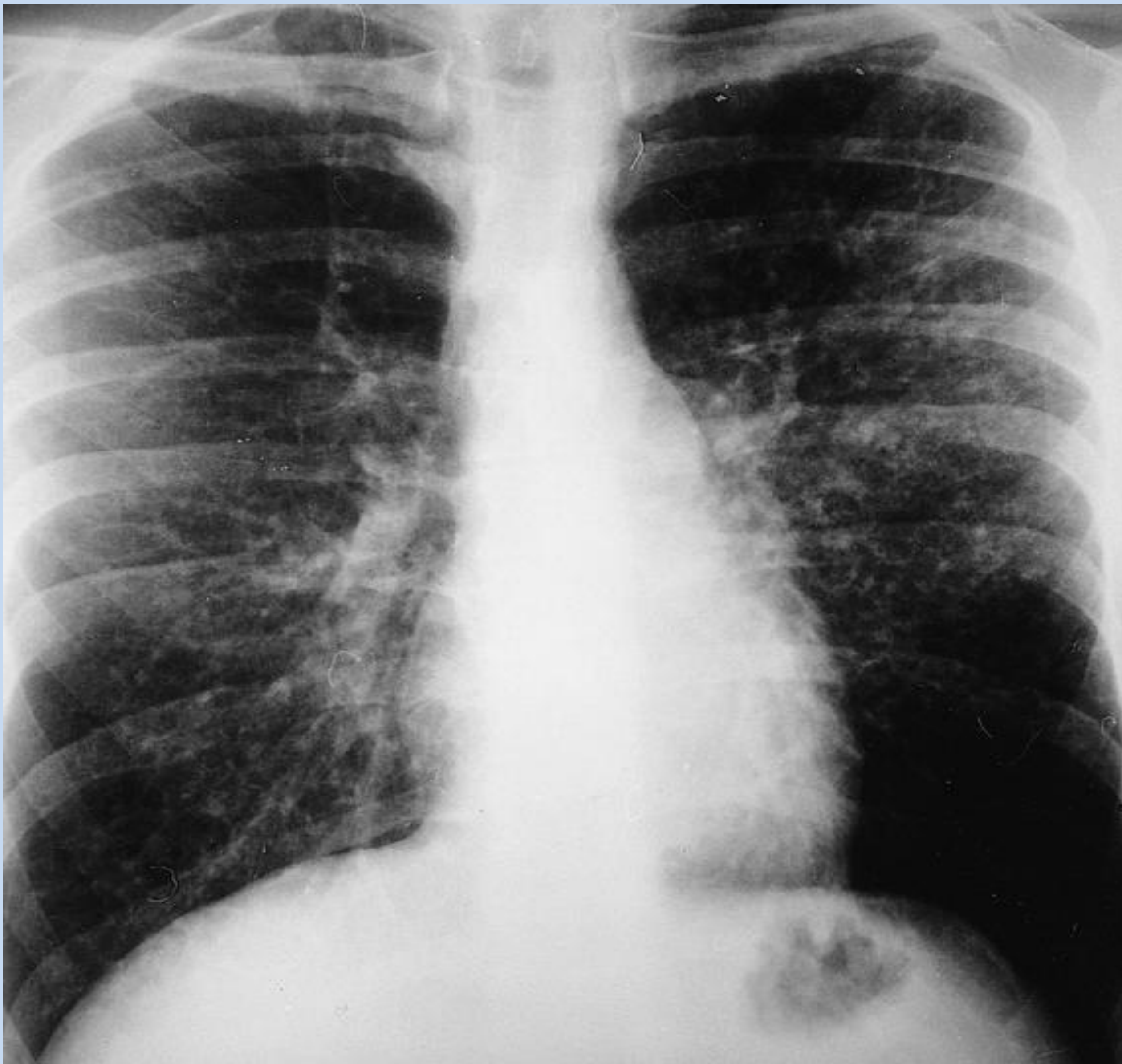


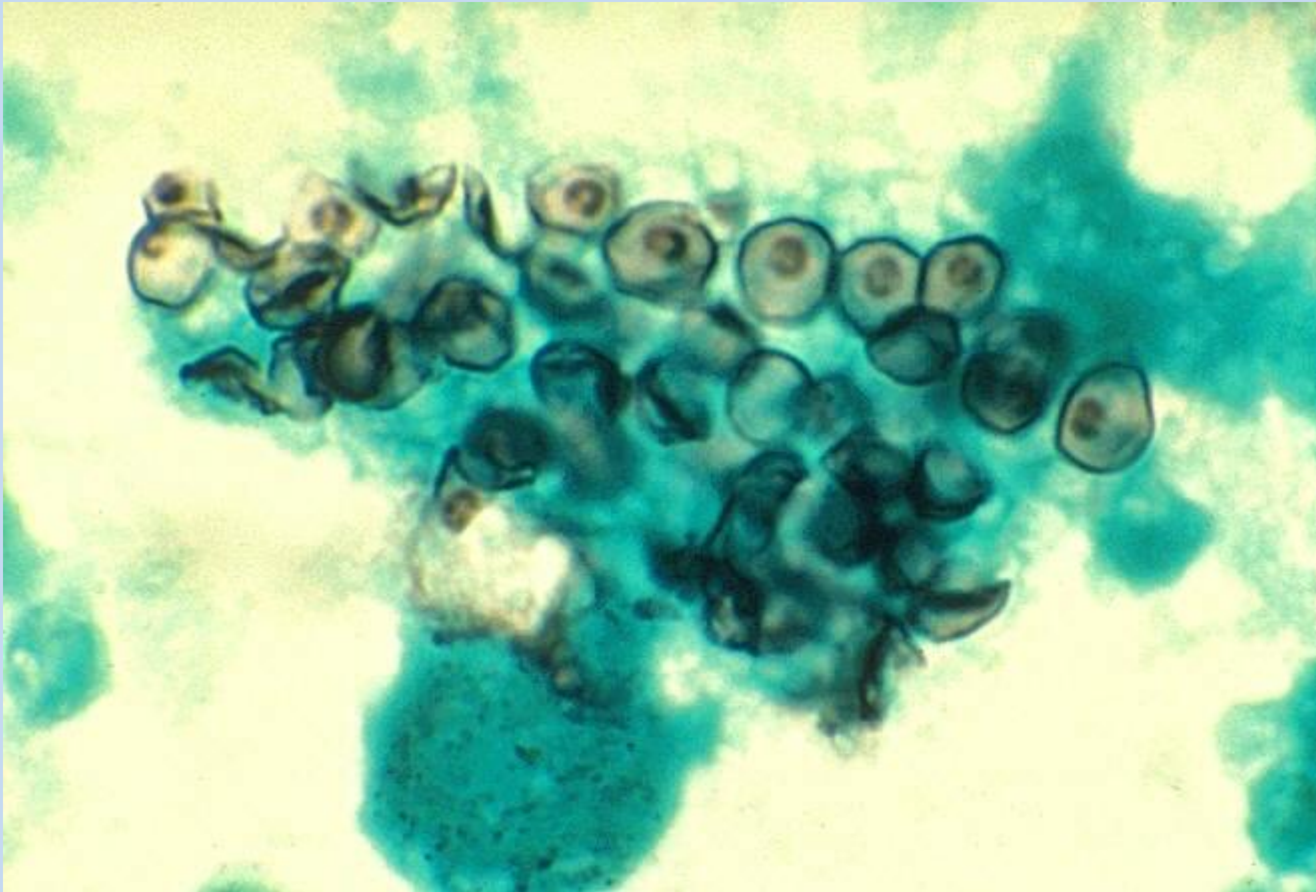
With CD4<200 and no HIV meds, no prophylaxis -

70-80% will develop PCP

Diagnosis of PCP

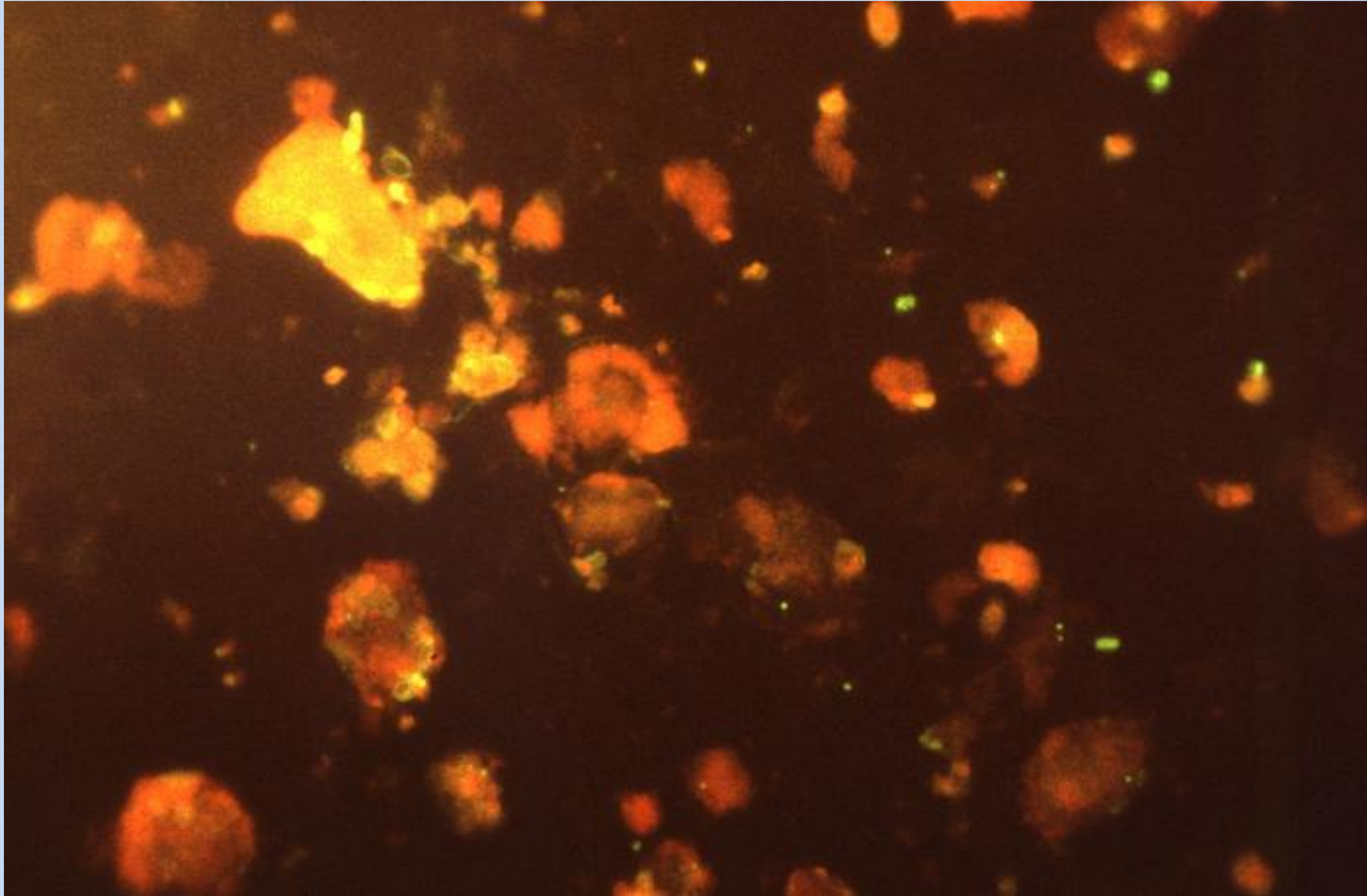
- Presumptive – with classic presentation
  - response to empiric therapy for PCP
  - thin-slice CT – patchy ground-glass attenuation
  - gallium scan – diffuse uptake both lungs
- Definitive:
  - **Histologic confirmation on induced sputum or BAL samples**
  - variety of stains available; nucleic acid 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

Source	**sensitivity**
Induced sputum	< 50% - 90%
BAL**	90 – 99%
Trans-bronchial Bx	95 – 100%
Open lung bx	95 - 100%

Early BAL allows focused therapy (1-2 drugs instead of 7), ID of co-infection(s), & earlier release from isolation.

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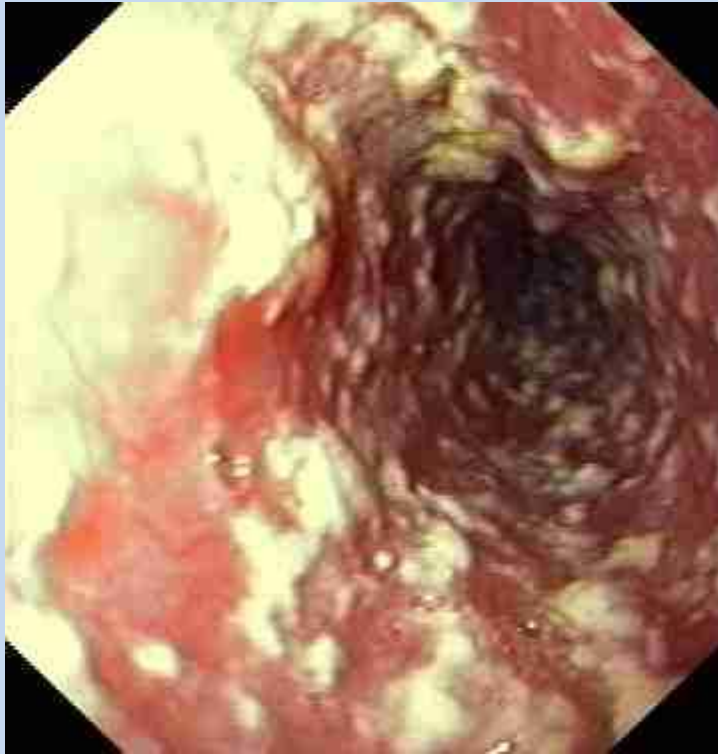
Case # 3: A 33-y/o Woman Walks into Your Clinic as a New Patient



Courtesy of CDC

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

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.

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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)

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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**

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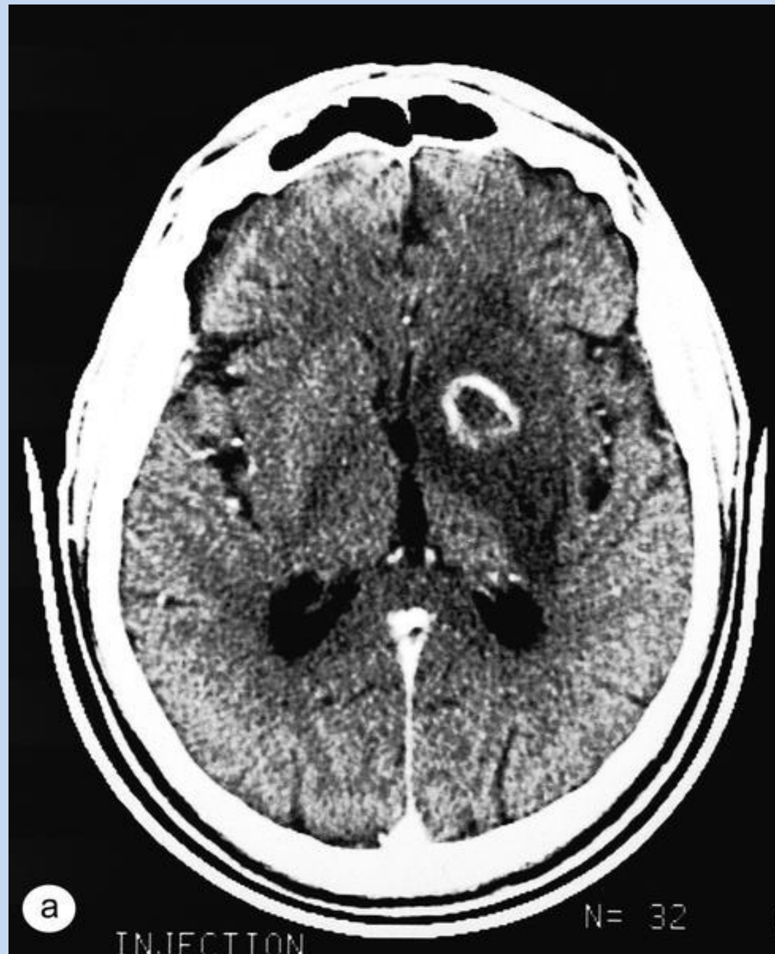
Case # 4: Which of the following statements is FALSE?

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)

- -Toxoplasmic encephalitis*
- -TB
- -PML (fever absent)
- -Primary CNS lymphoma*
- -Cryptococcal meningitis

- Bacterial abscess
- Chagas disease
- Brain tumors
- (Other fungal infections)

Symptoms:

- -headache and fever, focal encephalitis, confusion, motor weakness
- -PML – insidious focal neurologic defects (no fever)

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Dx: Toxoplasmic 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

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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

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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

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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

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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

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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

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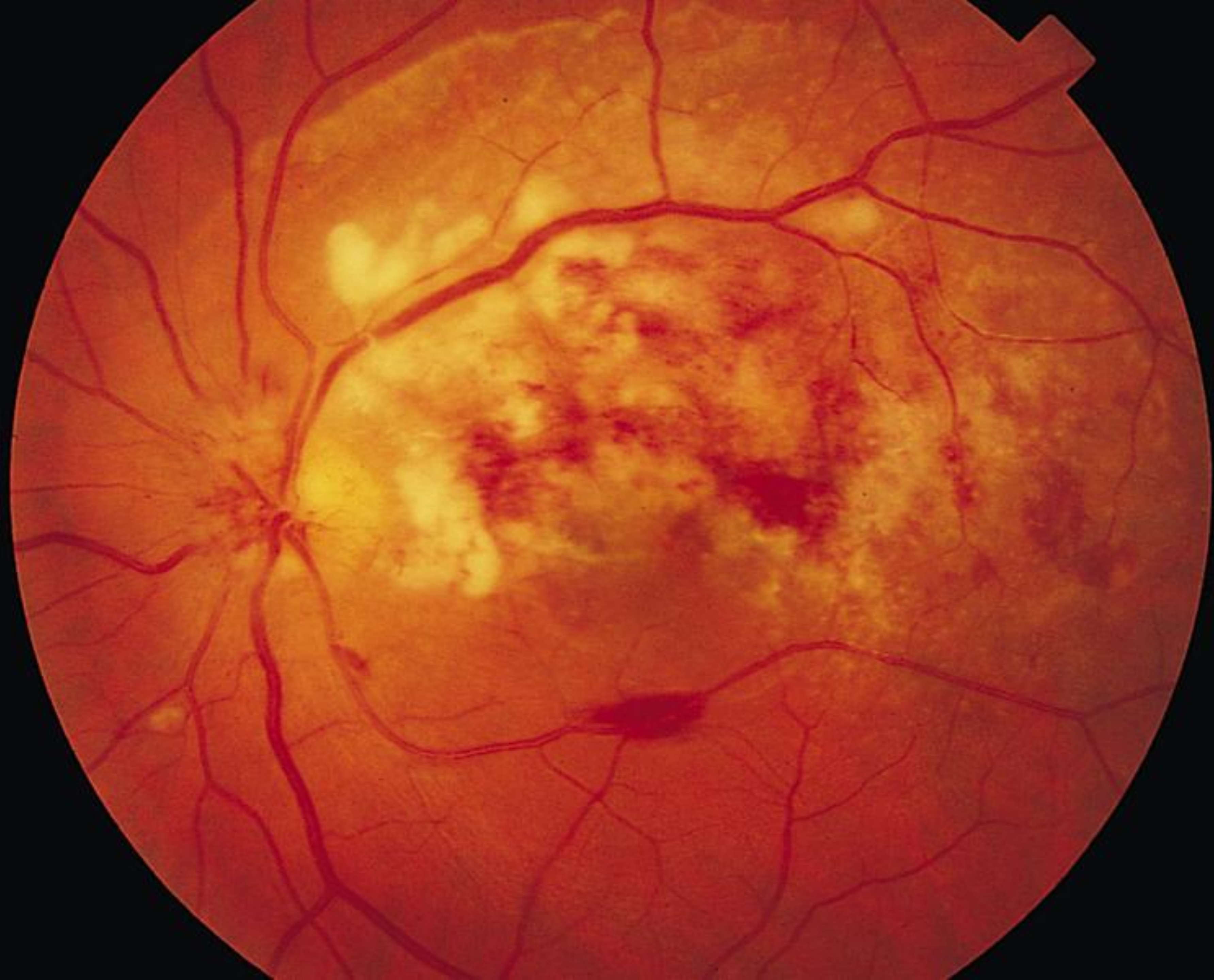

CMV Disease in HIV

- 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)

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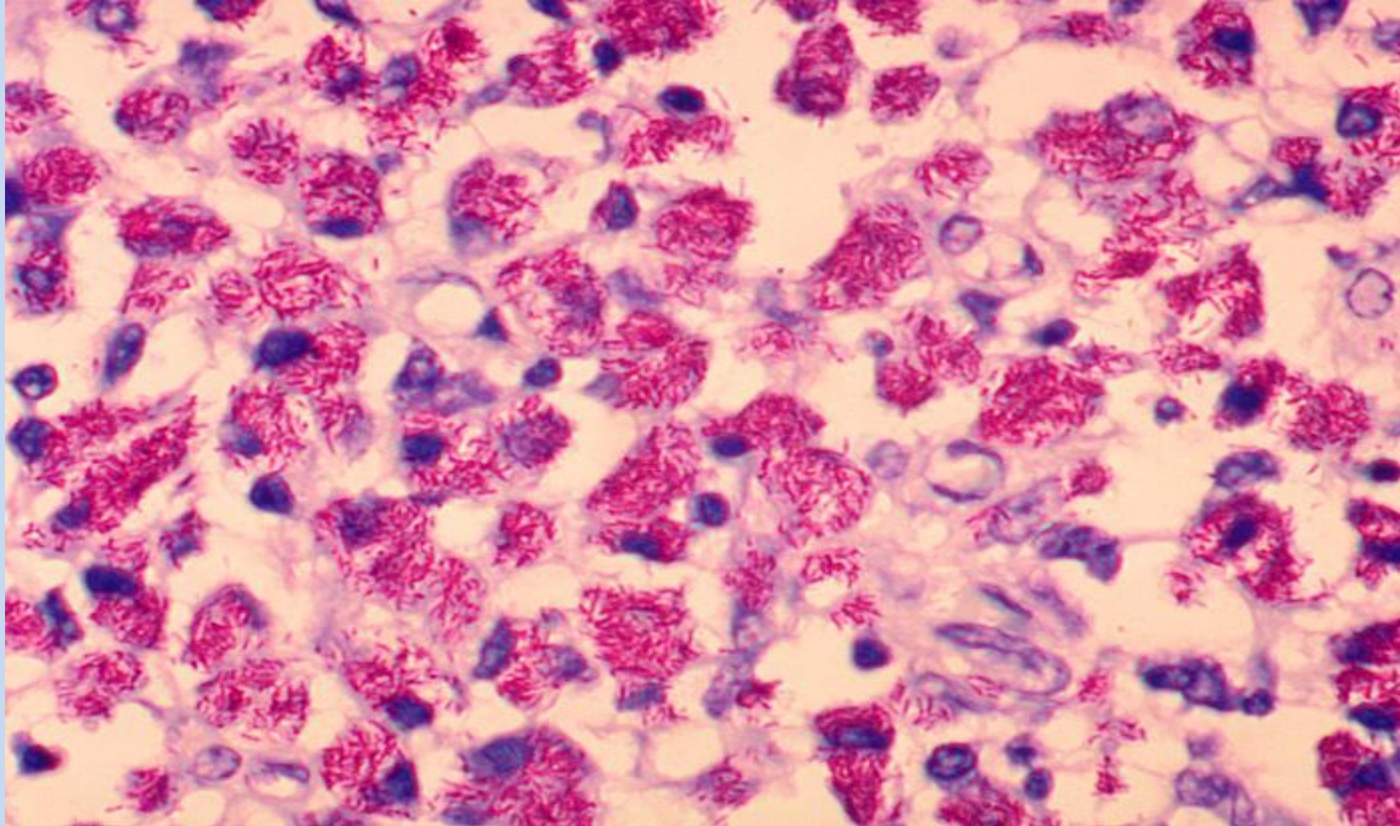
Do You Recognize This?

(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

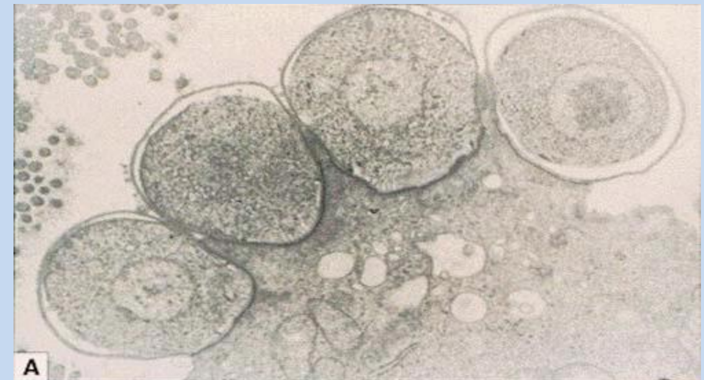
- Viral
  - Cytomegaloviral colitis
  - HIV enteropathy
  - KS of the bowel
- Parasitic
  - ***Cryptosporidium***
  - *Isospora belli*
  - *Cyclospora*
  - **Microsporidial species**
  - Giardia lamblia
  - Entamoeba
- Bacterial
  - *Salmonella*
  - *Shigella*
  - *Yersinia*
  - *Campylobacter*
  - Mycobacterial
  - *Clostridium difficile*
- Fungal
  - Candidal overgrowth of the large bowel

Cryptosporidiosis

- Spore-forming protozoa
  - # 1cause of protozoal diarrhea worldwide
- Intestinal infection
  - usually infects small bowel but also colon
  - profuse watery, large-volume stools, cramps
  - non-invasive: may infect gallbaldder
- 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



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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 (cryptosporidiosis 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