Question #1

A 50 year old male has HIV (CD4=40 cells/uL and HIV viral load =600,000 copies/uL) has central nervous system toxoplasmosis documented by a compatible CT of the head and a positive CSF PCR for toxoplasma. The patient also has cryptosporidiosis with 4 stools per day plus considerable nausea and thus has limited food intake. The pharmacy cannot obtain sulfadiazine or pyrimethamine.

The best option for therapy of the toxoplasmosis would be:

A. Atovaquone
B. Clindamycin plus primaquine
C. Trimethoprim-Sulfamethoxazole
D. Azithromycin plus Doxycycline
E. Nitazoxanide

Question #2

A 39 year old female from Brazil presents to an ER with a seizure. Her CT scan is shown. Her HIV serology is positive:
- CD4 = 20/µL
- VL = 100,000 copies/µL

It is thought to be unsafe to perform an LP.

She is started on sulfadiazine and pyrimethamine.

ARVs are held until her acute problem is under control.

After 10 days, she has not improved and a brain biopsy is performed (see image).
Question #2
What is the most likely diagnosis?
A. Toxoplasmosis
B. Cysticercosis
C. Leishmaniasis
D. Trypanosomiasis
E. Acanthamoeba

Trypanosoma cruzi
Blood Smear and CSF

Incidence of Toxoplasmosis
- Common (30%) before ART and chemoprophylaxis
- Seroprevalence in General Population
  - US-20%
  - Some areas of Europe, Africa: 80%
- Disease "never" occurs in seronegative patients except
  - Acute infection
  - Insensitive assay
  - Loss of ability to make antibody

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Transmission of Toxoplasma

- Feline feces (cats, but also lions etc)
  - Oocysts begin to be excreted 20 - 24 days post infection
  - Excretion persists 7 - 21 days
- Rare Meat (Lamb>Beef>Pork)
- Unusual
  - Raw shell fish, goat milk (reported 2009-2010)
  - Iatrogenic
  - Transplant, chemotherapy, radiotherapy
- Congenital
  - Acute acquisition by mother during gestation
  - Chronic infection in immunosuppressed mother

Clinical Manifestations of Toxoplasmosis when Acquired Post-Partum

- Acute Infection
  - Asymptomatic (80-95%)
- Lymphadenopathic (5-10%)
- Chronic Latent Infection
  - Asymptomatic (Most)
  - Cerebral (Few)
- Disseminated
  - Abnormal Immunity
  - (HIV, lymphoma, etc)

CNS Toxoplasmosis

- Non Contrast CT
- Flair MRI

Evaluation of CNS Mass Lesions in Patients with HIV/AIDS

- Radiologic Results
  - Non-specific although certain features suggestive
  - Look for Extra CNS lesions for biopsy
- Laboratory Studies to Perform
  - Serology: Toxo IgG, Toxo PCR
  - Serum Crypt Ag and Histo Ag
  - Blood culture: AFB, fungus
  - CSF: Crypt Ag
  - PCR (EBV, CMV, Toxo)
  - Urine: Histo Ag
- Response to Empiric Therapy

Empiric Diagnosis of CNS Toxo

- Compatible CT or MR plus
- CD4 Count <100 cells/uL plus
- Toxo IgG antibody positive plus
- Not on TMP-SMX prophylaxis plus
- Response to therapy within 2 weeks

Time to Neurologic Response

35 CNS Toxo Patients Treated with Clindamycin - Pyrimethamine

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Definitive Diagnosis of Cerebral Toxoplasmosis

- Brain biopsy
- Serum PCR
- CSF PCR

Therapy for Cerebral Toxoplasmosis

- **Preferred Regimen**
  - Sulfadiazine plus pyrimethamine plus leucovorin

- **Alternative Regimens**
  - Trimethoprim-sulfamethoxazole
  - Clindamycin plus pyrimethamine
  - Atovaquone +/- Pyrimethamine

Adjunctive Therapies for CNS Toxoplasmosis

- **Corticosteroids**
  - Not routine
  - Only if increased intracranial pressure/symptoms/signs

- **Anticonvulsants**
  - Not routine
  - Only after first seizure

Primary Prevention of Toxoplasmosis in Patients with HIV

- **Indication**
  - Positive IgG and CD4<100 cells/μL

- **Drugs**
  - First Choice
    - TMP-SMX (one ds qd)
  - Alternatives
    - Dapsone-Pyrimethamine
    - Atovaquone + Pyrimethamine

Primary Prevention of Toxoplasmosis in Patients with HIV

- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Protective against Toxo

- For patient on Aerosol Pentamidine or Dapsone for PCP prophylaxis
  - If on dapsone: add pyrimethamine
  - If on Aerosol pentamidine: not protected

Primary Prevention of Toxoplasmosis in Patients with HIV

- For patients with CD4<200 who are on TMP-SMX or atovaquone for PCP prophylaxis
  - Protective against Toxo

Non Tuberculous Mycobacterial Infections in HIV Infected Patients

You Need Microbiologic or Epidemiologic Clue on Exam!

- **Avium complex**
  - Dissemination

- **Hemophilum**
  - Cutaneous abscesses

- **Bovis**
  - Adenitis, Dissemination

- **BCG (Bovis)**
  - Dissemination

- **Genovense**
  - Dissemination

- **Scrofulaceum**
  - Adenitis, Dissemination

- **Xenopi**
  - Lung nodules or infiltrates

- **Malmoense**
  - Cavitary lung, CNS ring lesions

- **Chelonei**
  - Skin, Soft Tissue, Joint, Bone

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An HIV-infected patient is admitted to the hospital with three weeks of cough, fever, 25 lb weight loss, and anorexia. He is found to be HIV infected and to have a CD4 count <10 cells/µL and VL = 500k.

- His chest x-ray shows diffuse interstitial infiltrates
- BAL = PCP by immunofluorescence

Two weeks later while the patient is still in the hospital due to disposition issues, the lab reports:

- Three blood cultures and the BAL are growing a mycobacterium
- Probe = Mycobacterium avium complex

What type of isolation is appropriate?
A. None
B. Droplet
C. Respiratory
D. Contact
E. Contract and droplet

**Answer #3**

- **No isolation**

Atypical mycobacteria, including M. avium complex, are not transmitted from person to person. They are acquired from environmental sources including food, dust, dirt, animals, and enter the human by a GI or respiratory route.

M. Avium is almost never the cause of pulmonary disease in HIV infected patients. In this case the M. avium, like CMV, was likely present in the lung and because the organism can be shed in various locations in HIV infected patients with low CD4 counts. MAC causes bacteraemia, adenitis, enteritis, hepatosplenomegaly, but not pneumonitis in this patient population.

ART should be started within two weeks of documenting the initial PCP and MAC. The MAC should be treated with azithromycin plus ethambutol +/- rifabutin pending macrolide susceptibility testing.

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**Mycobacterium Avium Intracellulare Complex**

- **Epidemiology**
  - Ubiquitous in dirt, animals etc

- **Transmission**
  - Respiratory via dust
  - GI via food, water
  - Person-to-person unlikely
  - Environmental isolates correlate poorly with human isolate

**Mycobacterium Avium Intracellulare**

- **Risk factors**
  - CD4 < 50 or High VL
  - Colonization: GI / respiratory

- **Incidence pre ART: 20-40% (North America)**
  - Now declining with ART and probably non-ART related factors

- **Acute Disease: Clinical manifestations**
  - Fever, wasting, nodes, liver, spleen
  - Rare as cause of lung disease
  - Lab: [Alk Phos, Hg], Albumen

**Mycobacterium Avium Intracellulare Diagnosis**

- **Source of Isolates**
  - Blood
    - Bactec (7-14 days)
  - Sputum/Stool/Urine
    - Low predictive value

- **Lab Identification**
  - Specific DNA Probes for specimens' cultures
  - MALDI-TOF

**MAC: Susceptibility Testing**

- **Recommended for primary isolates**
  - Clari and Azithro

- **Other drug testing not validated for MAC**
Treatment for MAC

- **Antiretroviral Therapy**
  - Start within 2 weeks of anti-mac therapy

- **Specific Therapy**
  - Clarithro (or Azithro) + Ethambutol
  - Rifabutin optional 3rd drug use if severe disease
  - Beware drug interactions with clar or rifabutin

**Response**
- Fever should decline within 2-4 weeks
- Blood cultures should be negative in 2-4w
- Repeat blood cultures only if symptoms

**Stop chronic suppression**
- CD4 > 100 x 6M, axa and therapy >12 m

Salvage Therapy for MAC

- **Not For Boards**
- No evidence-based standard
- Logical to be guided by in vitro susceptibility testing
  - Not standardized for MAC other than macrolides
  - Options: Amikacin, Ciproflox, Moxiflox, Mefloquine, Linezolid, Bedaquiline

MAC Prophylaxis 2020

- Primary prophylaxis against disseminated MAC disease is **not** recommended if ART initiated immediately (AII).
- Primary MAC prophylaxis, if previously initiated, should be discontinued if person is on ART (AI).

Immune Reconstitution Inflammatory Syndrome

- **Definition**
  - Worsening manifestations or abrupt/atypical presentation of infection or tumor when ART started
  - Paradoxical-manifestation of pre-existing infection or tumor
  - Unmasking-manifestation of previously occult infection/tumor

- **Timing**
  - Few days to 6 months
  - Viral load drop more relevant than CD4 rise
  - (better lymphocyte function>number)
59 - Management of AIDS-Related Opportunistic Infections II

Speaker: Henry Masur, MD

**Immune Reconstitution Inflammatory Syndrome**

- **Predictors**
  - Pre therapy low CD4 or high VL
  - Prior OI or short therapy for OI
  - High pathogen load

- **Outcome-Morbidity Can Be Severe**
  - Obstructed bowel, biliary tract, ureter, bronchus
  - Myocarditis, meningeal inflammation/increased ICP, serositis (pleura, peritoneum, pericardium)

**Pathogens Commonly Associated with IRIS**

- Mycobacterium avium complex
- Mycobacterium tuberculosis
- Cryptococcus neoformans
- Many others
  - CMV retinitis, HBV
  - Mucocutaneous HSV and VZV
  - PCP, Histi
  - PML
  - KS

**Management of IRIS**

- **Reassess Diagnosis**
  - Evaluate for concurrent, additional OIs and tumors
  - IRIS Diagnosis of exclusion

- **Treat IRIS**
  - Continue ART
  - Treat identified pathogen-usual practice without data
  - NSAIDS or Coritcosteroids
  - Prednisone 20-40mg qd x 4-8 weeks

**MAC IRIS in Patient with HIV**

**CT Scan: Pleural-Based MAC**
Life Threatening IRIS – How Would They Test for These?

- Unmasking
  - Unrecognized lymphadenitis due to TB, MAC, Fungi
  - Unrecognized cryptococcal meningitis
  - Unrecognized CMV retinitis
  - Inflammation of Kaposi sarcoma skin lesion
  - Pulmonary infiltrates due to PCP, fungi, TB
- Exacerbation of Crypt Meningitis Increased intracranial pressure
  - New focal findings
- Transaminase Flair in Patient with Untreated HBsAg or HBcoreAb
  - Transaminase flair due to HBV
- Exacerbation of previously treated CMV retinitis, PCP, TB

Question #4

What advice do you give the lab and hospital epi?

A. This should grow at 37°C
B. This should grow on conventional TB culture media
C. This most likely was acquired by acupuncture or some other manipulation.
D. This is treatable with trimethoprim-sulfamethoxazole
E. This can be cultured only at 32°C with iron enriched medium

Fungal Diseases in HIV-Infected Persons

- Candidiasis
- Cryptococcosis
- Histoplasmosis
- Coccidiomycosis
- Talaromyces

Skin Lesions HIV-Difficult to Distinguish
HIV-Related Cryptococcal Meningitis

- **Clinical Presentation**
  - CNS manifestations typically develop over several weeks (median 2 weeks)
  - Crypt IRIS is typically more acute
  - Only 25% of those with positive CSF develop meningeal signs and symptoms
  - Most HIV related cases have extrameningeal involvement including fungemia
  - CD4 count < 100 cells/mm³
    - 90% cases

**Diagnosis of Cryptococcal Disease**

- **CSF**
  - Often minimal abnormalities with lymphocyte pleocytosis
    - But... can be negative with early disease when blood Cr Ag +
  - Opening pressure >20-25cm H2O 60-80%
- **Blood Culture positive**
  - 60% of patients with clinical meningitis
  - Growth in < 7 days

**Antigen Tests for Cryptococcal Disease**

- **Blood, Serum, Plasma, CSF:**
  - Antigen Latex Agglutination or
  - Enzyme Linked Immunoassay (EIA)
    - False positive rarely occurs
      - Trichosporon, Capnocytophaga, various chemicals
  - Cryptococcal Lateral Flow Assay (IMMY LFA)
    - Dipstick test for blood and CSF
    - Four fold higher titers than Latex Aggl or EIA
    - Good sensitivity and specificity

**PCR Tests for Cryptococcal Disease**

- **C. neoformans and C. gatti**
  - **PCR for CSF**
    - Screening test available in multiplex assays
      - False negatives and false positive reported
    - Simultaneous antigen test should be performed if cryptococcal meningitis is suspected
      - May be useful for distinguishing
        - IRIS (PCR neg)
        - Relapse (PCR positive)

**Therapy of Cryptococcal Meningitis**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal Ampho B plus Flucytosine*</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Flucytosine 400 mg po qd</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Fluconazole 200 mg po qd</td>
<td>&gt;52 weeks**</td>
</tr>
</tbody>
</table>

*5FC Associated with earlier sterilization CSF, fewer relapses
**Stop after 12 in total therapy if CD4 >100-150 or >3m, Asymptomatic, VL <50 copies

**Question #5**

Patient presents with cryptococcal meningitis, severe headache, and opening pressure >25 cm H2O on day 1 of therapy

Which of the following would you initiate if the CNS symptoms persist on day 2

- A. Dexamethasone
- B. Acetazolamide
- C. Mannitol
- D. Lumbar puncture to remove fluid
- E. Lumbar puncture for repeat diagnostic studies and MRI to assess for a second, concurrent infectious or neoplastic process
59 - Management of AIDS-Related Opportunistic Infections II
Speaker: Henry Masur, MD

Elevated CSF Pressure
- 75% of patients have Opening Pressure >20 cm CSF
  - Abnormal = >25 cm CSF
  - Left lateral decubitus, flat position
- Symptoms
  - Blurred vision, confusion, obtundation
- Management: If symptomatic and >25cm
  - Remove volume to reduce pressure by half or <20cm H2O
  - Continue Lps daily for symptomatic patients until stable for at least 2 days
  - Shunt if regular Lps required for “many” days
- Not routinely recommended
  - Corticosteroids, Mannitol, Acetazolamide

Monitoring Therapy for Cryptococcal Meningitis
- During Therapy
  - Serial testing of blood or CSF Crypt Ag during therapy is not useful
  - Negative serum or CSF Ag is NOT required for termination of therapy
- Post Therapy CSF Culture
  - Advocated by some to determine likelihood of relapse

Commonly Asked Questions
- Liposomal Amphotericin B Induction for < 14 days
  - No (not yet)
- Fluconazole based regimens in US As Initial Rx
  - No-not as effective as Ampho
  - Efficacy depends on dose of fluconazole

Asymptomatic Cryptococcal Antigenemia
(Pre-emptive Therapy for Crypt Ag +/Low CD4)
- Recommendation: Optional in US
  - Screen patients with CD4<50-100
  - 2.0% of all patients positive, and 4.2% of patients with CD4< 50
  - Positive serum or CSF predicts development of active disease
- If Positive: Perform LP and Blood Cultures
  - If CSF positive
    - Treat like crypt meningitis/disseminated (Ampho/5FC)
  - If CSF negative
    - Treat with fluconazole x6 months

Histoplasmosis
- Clinical Presentation
  - CD4>200 cells/ul
  - Focal disease like immunocompetent
  - CD4<200 cells/ul
  - Disseminated disease:
    - Fever, weigh loss, fatigue, hepatosplenomegaly
    - Meningitis, Septic Shock, GI manifestations also common
- Diagnosis
  - Antigen detection
  - BAL antigen also useful
  - Cultures useful but….takes several weeks to grow

Talaromyces – Formerly Penicilliosis marnefii
- Rarely if Ever Seen in US
- Common in Asia transmitted by Bamboo Rat or Abiotically
- Serum antigen test (research) sensitive and specific
- Treat with Ampho or Itraconazole

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CMV Syndromes

- Retinitis
- Colitis
- Ventriculitis
- Radiculopathy, Myelitis, Mononeuritis Multiplex
- Esophagitis (uncommon)
- Adenitis (rare)
- Pneumonia (rare)

Diagnosis of HIV Related CMV Disease

- Serology
  - Disease unlikely if IgG seronegative
  - Rarely done
- Cytology
  - Rarely useful
- PCR
  - Correlates with CD4 Count
  - “Low sensitivity and specificity” for clinical disease

Diagnosis of CMV Retinitis

Funduscopic exam
- PCR of blood not useful: 70% sensitive, very non specific
- Vitreal taps for diagnosis with PCR rarely necessary
  - Tap positive in 80% of cases

CMV Retinitis

- Lesion border: tiny dry-appearing, granular, dot-like “satellites” at the interface between infected and normal retina
- Little inflammation of the vitreous humor unless IRIS
- Blood vessels near the lesions may appear to be sheathed
- Progression is usually slow-months unless retinal detachment
- Effect on vision depends on location
  - Peripheral lesions often inapparent
  - Macula or optic disk involvement is clinically apparent and can be catastrophic
Therapy for CMV Retinitis
Ganciclovir intraocular implant no longer available!

- Immediate sight-threatening lesions
  - ART
  - IV Ganciclovir or Valganciclovir 900 mg PO (bid x 14–21 days), then qd plus
  - Intravitreal ganciclovir x 4-7 doses over 1-2 weeks
  - Injections can be associated with infections or retinal detachment and hemorrhage
- Small peripheral lesions
  - ART
  - Oral valganciclovir
  - +/-intravitreal ganciclovir

Failure of CMV Therapy

- Early Failure-rarely due to CMV resistance
  - Wait at least 10-14 days to see clinical or laboratory response
- Late Failure
  - UL97 (phosphotransferase gene) mutation
    - Low level: no cross resistance to Foscarnet, Cidofovir
    - Many respond to high dose GCV (10mg/kg q 12 h)
  - UL54 (polymerase gene) mutation
    - High level: cross resistant to cidofovir and some are cross resistant to Foscarnet depending on precise mutation

Salvage Therapy for CMV Retinitis

- Systemic Options
  - Ganciclovir higher dose
  - Foscarnet IV
  - Foscarnet IV plus Ganciclovir IV
  - Cidofovir IV
- Intraocular
  - Ganciclovir or Foscarnet

Thank You