

Opportunistic Infections

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Objectives:

After reviewing this material and attending lecture, the student should be able to

- 1) Define an opportunistic infection (OI).
- 2) Recommend an appropriate treatment for the following OIs, given diagnosis and relevant patient information
 - a. PCP
 - b. Toxoplasmosis
 - c. MAC disease
 - d. Cryptococcal Meningitis
 - e. Histoplasmosis
- 3) Recommend appropriate primary or secondary prophylaxis, if given relevant information for a patient.
- 4) Identify monitoring parameters to evaluate the patient's treatment for a given OI.

1) Definition

- a) Opportunistic infection (OI) =
- b) Examples of persons at risk for OIs
 - HIV/AIDS
 - Cancer
 - Immunosuppressive drugs
 - ◇ Long-term, high-dose corticosteroids
 - ◇ Chemotherapy
 - ◇ Immunosuppressive drugs used for stem cell and organ transplants
- c) Examples of OIs
 - Bacterial pneumonias
 - Tuberculosis
 - Aspergillosis
 - Cryptococcus
 - *Pneumocystis jiroveci* pneumonia
 - Syphilis
 - Cryptosporidiosis
 - Cytomegalovirus (CMV) disease
 - Histoplasmosis
 - Mucocutaneous candidiasis
 - *Mycobacterium avium* complex disease
 - Hepatitis B and C

2) Treatment versus prophylaxis

- a) Prophylaxis = trying to prevent disease for which the patient is at risk
 - Primary prophylaxis
 - ◇
 - Secondary prophylaxis
 - ◇
- b) Treatment = eradicate/control organism causing infection and eliminating signs and symptoms of disease

3) *Pneumocystis jiroveci* pneumonia (PCP)

- a) Cause
 - *Pneumocystis jiroveci* (fungal organism), previously called *P. carinii*
- b) Transmission
 -
 - Airborne transmission (?)
- c) Signs/symptoms
 - 90% of cases in those with
 - Progressive over days to weeks
 - ◇ Exertional dyspnea
 - ◇ Fever
 - ◇ Nonproductive cough
 - ◇ Chest discomfort
 - Oral thrush is a common co-infection
 - Labs

- ◇ PaO₂ at room air
 - ◆ PaO₂ > 70 mm/Hg:
 - ◆ PaO₂ ≤ 70 mm/Hg:
- ◇ LDH > 500 mg/dL
- ◇ Chest X-ray
 - ◆ Early on, X-ray will appear normal
 - ◆ Later in disease, will see diffuse, bilateral infiltrates; no cavitation or pleural effusion
- ◇ CT scan
 - ◆ Ground-glass attenuation
 - ◆ Usually will show abnormalities that are not seen on X-ray with mild to moderate cases

d) Diagnosis

- Culture of organisms
 - ◇ Bronchoalveolar lavage fluid (BALF)
 - ◇ Induced sputum
- Sensitivity of culture depends on method used and technique
 - ◇ Induced sputum: < 50% - >90%
 - ◇ Bronchoscopy with BALF: 90 – 99%
 - ◇ Transbronchial biopsy: 95 – 100%
 - ◇ Open lung biopsy: 95 – 100%

e) Treatment

- Length of therapy (LOT):
- ART is usually delayed for at least 2 weeks if not until after treatment is completed

First-Line Therapies	Alternative Therapies
Trimethoprim-sulfamethoxazole (TMP-SMX) Dosing is based on trimethoprim component PO dose usually works out to be TMP/SMX DS 2 tabs TID	Pentamidine (severe cases) 4 mg/kg IV qday
Corticosteroids <i>Indicated only for severe cases of PCP</i> Prednisone 40 mg BID x 5 days Prednisone 40 mg qday x 5 days Prednisone 20 mg qday x 11 days (IV methylprednisolone = 75% of PO prednisone dose) Should be started within 72 hours of starting antibiotic treatment	Primaquine and clindamycin (mild to moderate cases) P 15 – 30 mg base PO qday + C 300 – 450 mg PO qday ÷ 3 – 4 doses (If consider IV clindamycin, dose is 600 – 900 mg/day ÷ 3 – 4 doses)
	Dapsone and trimethoprim (mild to moderate cases) D 100 mg PO qday + T 15 mg/kg/day ÷ 3 doses (PO)
	Atovaquone (mild cases) 750 mg PO BID with food

f) Prophylaxis

First-Line Therapies	Alternative Therapies
	Dapsone 50 mg PO BID or 100 mg PO qday
Trimethoprim-sulfamethoxazole (TMP-SMX) TMP-SMX SS 1 tab qday	Atovaquone 1500 mg PO qday
	Trimethoprim-sulfamethoxazole (TMP-SMX) TMP-SMX DS 3x/ week
	Dapsone and Pyrimethamine and Leucovorin D 50 mg PO qday + P 50 mg PO qweek + L 25 mg PO qweek <u>OR</u>

	D 200 mg PO + P 75 mg PO + L 25 mg PO, all qweek (Consider if intolerant of TMP-SMX and want to cover toxoplasmosis as well)
	Pentamidine, aerosolized 300 mg q month (nebulized with Respigard nebulizer)

- When to start?
 - ◇ Primary prophylaxis
 - ◆
 - ◆ CD4% < 14%
 - ◆ Diagnosis of oropharyngeal candidiasis
 - ◆ History of AIDS-defining illness
 - ◇ Secondary prophylaxis
 - ◆
- When to stop?
 - ◇ Primary prophylaxis
 - ◆
 - ◇ Secondary prophylaxis
 - ◆
 - ◆ Consider for life if PCP episode at CD4 > 200 cells/L

g) Monitoring

- Disease
 - ◇ Should see improvement in 4 – 8 days in ABGs, pulmonary function
 - ◆ If patient is not tolerating TMP/SMX due to common adverse effects, supportive care to treat adverse effects should be attempted first before changing regimen
 - (i) Rash – antihistamines
 - (ii) Nausea – antiemetics
 - (iii) Fever - antipyretics
 - ◆ If lack of improvement, consider adding to a regimen or switching regimen
 - ◆ If patient is not on corticosteroids, patient may worsen initially in 3 – 5 days due to inflammatory response
 - (i) Should still wait up to 8 days to monitor progress
 - ◆ If fail TMP-SMX for moderate-to-severe cases, consider using
 - (i) Pentamidine
 - (ii) Primaquine + clindamycin
 - (iii) No data has evaluated which one of these options is the best to switch to after TMP-SMX failure
 - ◆ If fail TMP-SMX for mild cases, consider using
 - (i) Atovaquone
- Drugs: See Table 1 at end of notes

4) Toxoplasmosis

a) Cause

- *Toxoplasma gondii*

b) Transmission

- Primary infection
 - ◇ eating undercooked meat with tissue cysts
 - ◇ exposure from cat feces that have sporulated
- Disease usually result of reactivation of latent tissue cysts

c) Signs/symptoms

- Usually seen in patients with
- Primary infection may either be acute cerebral disease (encephalitis) or disseminated disease
- Most common presentation =
 - ◇ Headache
 - ◇ Confusion
 - ◇ Motor weakness
 - ◇ Fever
 - ◇ Without treatment, disease will progress to seizures, stupor, and coma
 - ◇ Physical exam/ laboratory findings
 - ◆ Focal neurological abnormalities

- ◆ CT scan/ MRI
 - (i) Multiple contrast-enhancing lesions, often with edema

d) Diagnosis

- Immunological studies
 - ◇ Anti-toxoplasma IgG antibody positive
 - ◇ Lack IgM antibodies
- Definitive diagnosis (all bullets are required)
 - ◇
 - ◇
 - ◇
 - ◇
- ◆ Requires brain biopsy
 - ◇ Some may choose to use first three criteria after eliminating all other causes in the differential diagnosis, only choosing to do brain biopsy with failure to respond to therapy
- PCR of CSF
 - ◇ High specificity, low sensitivity
 - ◇ Once therapy started, will have negative results

e) Treatment

- LOT ≥

First-Line Therapies	Alternative Therapies
<p>P 200 mg PO x 1, then If weight < 60 kg: P 50 mg PO qday + S 1,000 mg q6h + L 10 -20 mg qday If weight ≥ 60 kg: P 75 mg PO qday + S 1,500 mg q6h + L 10 -20 mg qday (leucovorin may be increased up to ≥ 50 mg)</p>	<p>Pyrimethamine and leucovorin and clindamycin P 200 mg PO x 1, then If weight < 60 kg: P 50 mg PO qday + L 10 -20 mg qday + C 600 mg IV or PO q6h If weight ≥ 60 kg: P 75 mg PO qday + L 10 -20 mg qday + C 600 mg IV or PO q6h (leucovorin may be increased up to ≥ 50 mg)</p>
	<p>Trimethoprim-sulfamethoxazole 5 mg/kg TMP IV or PO BID</p>
	<p>Atovaquone and pyrimethamine and leucovorin P 200 mg PO x 1, then If weight < 60 kg: A 1500 mg PO BID + P 50 mg PO qday + L 10 -20 mg qday If weight ≥ 60 kg: A 1500 mg PO BID + P 75 mg PO qday + L 10 -20 mg qday (leucovorin may be increased up to ≥ 50 mg)</p>
	<p>Atovaquone and sulfadiazine A 1500 mg PO BID and S 1,000 – 1,500 mg PO q6h</p>
	<p>Atovaquone 1500 mg BID with meals</p>
	<p>Pyrimethamine and leucovorin and azithromycin P 200 mg PO x 1, then If weight < 60 kg: P 50 mg PO qday + L 10 -20 mg qday + A 900 – 1200 mg PO qday If weight ≥ 60 kg: P 75 mg PO qday + L 10 -20 mg qday + A 900 – 1200 mg PO qday (leucovorin may be increased up to ≥ 50 mg)</p>

- ◇ In addition to above therapies, may consider use of dexamethasone to avoid brain damage due to edema
 - ◆ Must consider effect of edema vs. effect of immunosuppression due to corticosteroids
 - ◆ D/C as soon as possible
- ◇ Antiseizure medications should be used in those patients with a history of seizures through acute therapy

f) Prophylaxis

- Primary prophylaxis

◇ What to start?

First-Line Therapies	Alternative Therapies
(Will provide coverage for both toxoplasmosis and PCP)	Trimethoprim-sulfamethoxazole (TMP-SMX) TMP-SMX SS three times per week
	Dapsone and Pyrimethamine and Leucovorin D 50 mg PO qday + P 50 mg PO qweek + L 25 mg PO qweek OR D 200 mg PO + P 75 mg PO + L 25 mg PO, all qweek (Consider if intolerant of TMP-SMX and want to cover PCP as well)
	Atovaquone 750 mg PO q6-12h ± (pyrimethamine 25 mg PO qday and leucovorin 10 mg PO qday) (Reserve as last line therapy; use only if other options are not feasible)

◇ When to start?



◆ If restarting, consider at CD4 < 100 – 200 cells/μL

◇ When to stop?



◇ Other considerations

- ◆ For those patients who are IgG negative, counsel on avoiding environmental exposure
 - (i) No raw/undercooked meats
 - (ii) Hand washing after meat preparation and gardening
 - (iii) Wash fruits and veggies before eating
 - (iv) Change cat litter daily, preferably someone who is HIV-negative

• Secondary prophylaxis

◇ What to start?

First-Line Therapies	Alternative Therapies
S 2000 – 4000 mg/day ÷ 2 or 4 doses + P 25 – 50 mg PO qday + L 10 – 25 mg PO qday	Clindamycin and Pyrimethamine and Leucovorin C 600 mg PO q8h + P 25 – 50 mg PO qday + L 10 – 25 mg PO qday
	Atovaquone 750 mg PO q6-12h ± (pyrimethamine 25 mg PO qday and leucovorin 10 mg PO qday) (Reserve as last line therapy; use only if other options are not feasible)

◇ When to start?



◆ If stopped, restart if CD4 < 200 cells/μL

◇ When to stop?

- ◆ May consider after
 - (i)
 - (ii)
 - (iii)

g) Monitoring

- Disease
 - ◇ Clinical and radiological improvement
 - ◇ Antibody titer changes are not helpful in monitoring therapy
 - ◇ Failure
 - ◆ Clinical, radiological deterioration within first week with adequate therapy
 - ◆ No clinical improvement seen within 2 weeks
 - (i) If not done previously, consider brain biopsy: if histopathologically confirmed, switch to alternative regimen
 - ◇ Recurrence is unusual as long as patient is compliant with therapy
 - ◇ Monitor for signs or symptoms of other OIs if on corticosteroids
- Drugs: See Table 1 at end of notes

5) *Mycobacterium avium* complex (MAC) disease

a) Cause

- *Mycobacterium avium*

b) Transmission

- Present in the environment, with prevalence varying in geographic region
- Infection due to inhalation, ingestion, or inoculation through respiratory or GI tract
- Unlikely transmission is person-to-person

c) Signs/ symptoms

-
- May manifest in several different ways: disseminated multiorgan infection or localized syndromes
- Disseminated multiorgan infections
 - ◇ Early symptoms may be minimal, present before disease is actually detectable
 - ◆ Fever
 - ◆ Night sweats
 - ◆ Weight loss
 - ◆ Fatigue
 - ◆ Diarrhea
 - ◆ Abdominal pain
 - ◇ Laboratory findings
 - ◆ Anemia
 - ◆ Elevated alkaline phosphatase
 - ◇ Physical exam
 - ◆ Hepatomegaly
 - ◆ Splenomegaly
 - ◆ Lymphadenopathy

d) Diagnosis

- Confirmed diagnosis (both are needed)
 - ◇
 - ◇
- Other helpful tests
 - ◇ AFB smear
 - ◇ Culture of stool or biopsy of material from tissue or organ
 - ◇ Radiographic imaging of abdomen or mediastinum for detection of lymphadenopathy

e) Treatment

- LOT:
-
- Susceptibility testing should be performed for all isolates
-
- ◆ Consider increasing number of drugs to three or four for patients with advanced immune suppression (CD4 < 50 cells/ μ L), high mycobacterial loads (> 10² cfu/ mL of blood), or absence of effective ART

First-Line Therapies	Alternative Therapies	Additional Drugs to Consider Adding
	Azithromycin 500 – 600 mg PO qday	Rifabutin 300 mg PO qday
		Ciprofloxacin 500 -750 mg PO qday
		Levofloxacin 500 mg PO qday
		Amikacin 10 – 15 mg/kg IV qday
		Moxifloxacin 400 mg PO qday
		Streptomycin 1 g IV/IM qday

f) **Prophylaxis**

- Primary prophylaxis
 - ◇ Need to rule out subclinical MAC or tuberculosis prior to starting therapy
 - ◇ What to start?

First-Line Therapies	Alternative Therapies
	Rifabutin 300 mg PO qday
Clarithromycin 500 mg PO BID	

- ◇ When to start?
 - ◆
 - ◆ If restarting, consider with CD4 < 50 cells/μL
- ◇ When to stop?
 - ◆

- Secondary prophylaxis
 - ◇ What to start?

First-Line Therapies	Alternative Therapies
	Azithromycin and ethambutol (and rifabutin) A 500 mg PO qday + E 15 mg/kg PO qday ± R 300 mg PO qday
C 500 mg PO BID + E 15 mg/kg PO qday ± R 300 mg PO qday	

- ◇ When to start?
 - ◆ Continuation of initial therapy
 - ◆ Restart when CD4 < 100 cells/μL
- ◇ When to stop?
 - ◆ May be at low risk for MAC if
 - (i)
 - (ii)
 - (iii)

g) **Monitoring**

- Disease
 - ◇ Improvement of fever, mycobacterial load in blood or tissue seen within
 - ◆ May be delayed with more extensive disease or advanced immunosuppression
 - ◇ Blood cultures should be taken at _____ if fail to have clinical response to appropriate therapy
 - ◆ Isolates from cultures should be tested for susceptibility to clarithromycin and azithromycin, as well as ethambutol, rifabutin, ciprofloxacin, levofloxacin, amikacin, moxifloxacin, streptomycin
 - ◇ Treatment failure

- ◆ Construct new multidrug regimen of at least two susceptible drugs
 - (i) Do not use clofazimine, even if susceptible (increased risk of death)
- ◆ Optimized ART
- Drugs: See Table 1 at end of notes

6) **Cryptococcal meningitis**

a) **Cause**

- *Cryptococcus neoformans var neoformans*

b) **Transmission**

- Ordinarily found in soil
- Inhalation of fungus

c) **Signs/ symptoms**

-
- Most cases present as meningitis, but up to 1/2 have disseminated disease with pulmonary involvement, presenting with cough, dyspnea, abnormal chest X-ray
- Meningitis presentation
 - ◇ Fever
 - ◇ Malaise
 - ◇ Headache
 - ◇ Neck stiffness (one-fourth to one-third of cases)
 - ◇ Photophobia (one-fourth to one-third of cases)
 - ◇ Increased ICP leads to lethargy, altered mentation, personality changes, and/or memory loss
- Laboratory and Physical Examination
 - ◇ CSF
 - ◆ Mildly elevated serum protein
 - ◆ Normal to very low glucose
 - ◆ Elevated opening pressure (>200 mm of water)
 - ◇ Blood culture – up to 75% positive in meningitis

d) **Diagnosis**

-
-

e) **Treatment**

- Persons most at risk have CD4 < 50 cells/uL
- If left untreated, outcome is fatal
- Consider delaying ART for 2 weeks if high initial ICP
- First-line therapy for meningitis

First-Line Therapies	Alternative Therapies (for mild to moderate disease)
INDUCTION THERAPY x 2 weeks	INDUCTION THERAPY x 2 weeks
A 0.7 mg/kg/day IV q24h + F 25 mg/kg PO 4x/day	Amphotericin B 0.7 mg/kg/day IV
Liposomal amphotericin B + flucytosine LA 4-6 mg/kg/day IV q24h + F 25 mg/kg PO 4x/day	Amphotericin B deoxycholate + fluconazole A 0.7 mg/kg/day IV + F 400 mg PO/IV qday
	Fluconazole + flucytosine Flucon 400 – 800 mg/day (PO or IV) + Flucyto 25 mg PO 4x/day (This regimen should be used for 4 – 6 weeks)

CONSOLIDATION THERAPY x at least 8 weeks	CONSOLIDATION THERAPY x at least 8 weeks
	Itraconazole 200 mg PO BID

CHRONIC MAINTENANCE THERAPY	CHRONIC MAINTENANCE THERAPY
	Itraconazole 200 mg PO qday

f) Prophylaxis

- Primary prophylaxis
 - ◊ **Not recommended**
 - ◊ If used, may consider using fluconazole 100 -200 mg qday for patients with CD4 < 50 cells/μL
- Secondary prophylaxis
 - ◊ What to start?

First-Line Therapies	Alternative Therapies
	Itraconazole 200 mg qday

- ◊ When to start?
 - ◆ After completion of initial therapy
 - ◆ Restart if CD4 < 100 – 200 cells/μL
- ◊ When to stop?
 - ◆ May be at low risk for cryptococcal meningitis if
 - (i)
 - (ii)
 - (iii)
 - ◆ Some HIV specialists would prefer an LP with culture-negative results for CSF

g) Monitoring

- Disease
 - ◊ New symptoms, clinical findings after 2 weeks of treatment
 - ◆ Consider repeat LP
 - (i) Measure opening pressure
 - (ii) Should continue to monitor ICP during induction
 - 1. If continued increased ICPs, use therapeutic lumbar puncture or cerebral shunts for treatment
 - ◊ Successful induction treatment will result in significant clinical improvement and negative CSF culture
 - ◊ Having a positive lumbar puncture at 2 weeks indicates a higher risk of relapse
 - ◊ For those patients that have relapse
 - ◆ Must perform fungal culture
 - (i) Serum CrAg not reliable to indicate if disease or not in those that have been previously diagnosed
 - (ii) Consider relapse if increase in titer of 2 dilutions in comparison to convalescence CSF CrAg
 - ◆ Evaluate for relapse vs. IRIS, especially if ART started recently (usually within past 6 weeks but up to several months)
 - ◊ Consider resistance testing in patients with multiple recurrences in patients with adherence to therapy
- Drugs: See Table 1 at end of notes

7) Histoplasmosis

a) Cause

- *Histoplasma capsulatum*

b) Transmission

- Inhalation of organisms
- May be reactivation of latent infection in some patients
-

c) Signs/ Symptoms

- Those most at risk for disseminated disease for
 - Localized pulmonary infections tend to occur in immunocompetent patients (CD4 > 300 cells/μL)
 - Disseminated disease presentation
 - ◊ Fever
 - ◊ Fatigue
 - ◊ Weight loss
 - ◊ Up to 50% will have respiratory symptoms
 - ◆ Cough
 - ◆ Chest pain
 - ◆ Dyspnea
 - ◊ Less than 10% will present with septic shock, CNS, GI, or cutaneous manifestations

d) Diagnosis

-

- ◇ 95% sensitive in urine, 85% sensitive in serum
- ◇ Sensitive for disseminated histoplasmosis
- ◇ Insensitive for pulmonary infection
- May be isolated from blood, bone marrow, respiratory secretions, localized lesions
- ◇ Usually takes 2 – 4 weeks

e) Treatment

- Severe cases

First-Line Therapies	Alternative Therapies
ACUTE PHASE (2 weeks or until clinically improved)	ACUTE PHASE (2 weeks or until clinically improved)
	Amphotericin B deoxycholate A 0.7 mg/kg/day IV q24h
	Amphotericin B lipid complex A 5 mg/kg/day IV q24h

CONTINUATION PHASE (at least 12 months)	CONTINUATION PHASE (at least 12 months)
	Itraconazole oral solution 200 mg PO BID

- Less severe cases

First-Line Therapies	Alternative Therapies
Itraconazole 200 mg PO TID x 3 days, then 200 mg PO BID for at least 12 months	

- Meningitis
 - ◇ Liposomal amphotericin B 5 mg/kg/day for 12 – 16 weeks, then continue itraconazole 200 mg BID – TID for ≥ 1 year and until resolution of CSF findings
- Disease in patients with CD4 > 300 cells/ μ L
 - ◇ Consider treating as would be managed in an immunocompetent host

f) Prophylaxis

- Primary prophylaxis
 - ◇ Not routinely recommended
 - ◇ Should consider for patients that meet the following criteria
 - ◆
 - ◆ At high risk
 - (i)
 - (ii)
 - ◇ Persons with CD4 < 150 cells/ μ L do not necessarily need to be prophylaxed but should consider avoiding activities with an increased risk
 - ◆ Creating dust with working with surface soil
 - ◆ Cleaning chicken coops heavily contaminated with droppings or disturbing soil beneath bird roosting sites
 - ◆ Cleaning, remodeling, or demolishing old buildings
 - ◆ Disturbing areas with bird or bat droppings
 - ◆ Spelunking

- ◇ Therapies
 - ◆ Itraconazole 200 mg PO qday
- ◇ When to stop?
 - ◆ CD4 > 150 cells/μL after being on ART for 6 months
- Secondary prophylaxis
 - ◇ What to start?

First-Line Therapies	Alternative Therapies
	Amphotericin B 50 mg IV 1-2x/week (~ 0.7 mg/kg/day)

- ◇ When to start?
 - ◆ After completion of treatment phase
- ◇ When to stop?
 - ◆ Must meet the following requirements
 - (i)
 - (ii)
 - (iii)
 - (iv)
 - (v)

g) Monitoring Parameters

- Diseases
 - ◇ Monitor *Histoplasma* Ag every 3 – 6 months during therapy for evidence of continuing suppression
 - ◆ If on fluconazole, at least every 4 months, especially monitoring for possible increase due to resistance
- Drugs: See Table 1 at end of notes

Resources

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Adults and Adolescents – June 18, 2008. Recommendations of the National Institutes of Health, Centers for Disease Control and Prevention, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at <http://www.aidsinfo.nih.gov/Guidelines>