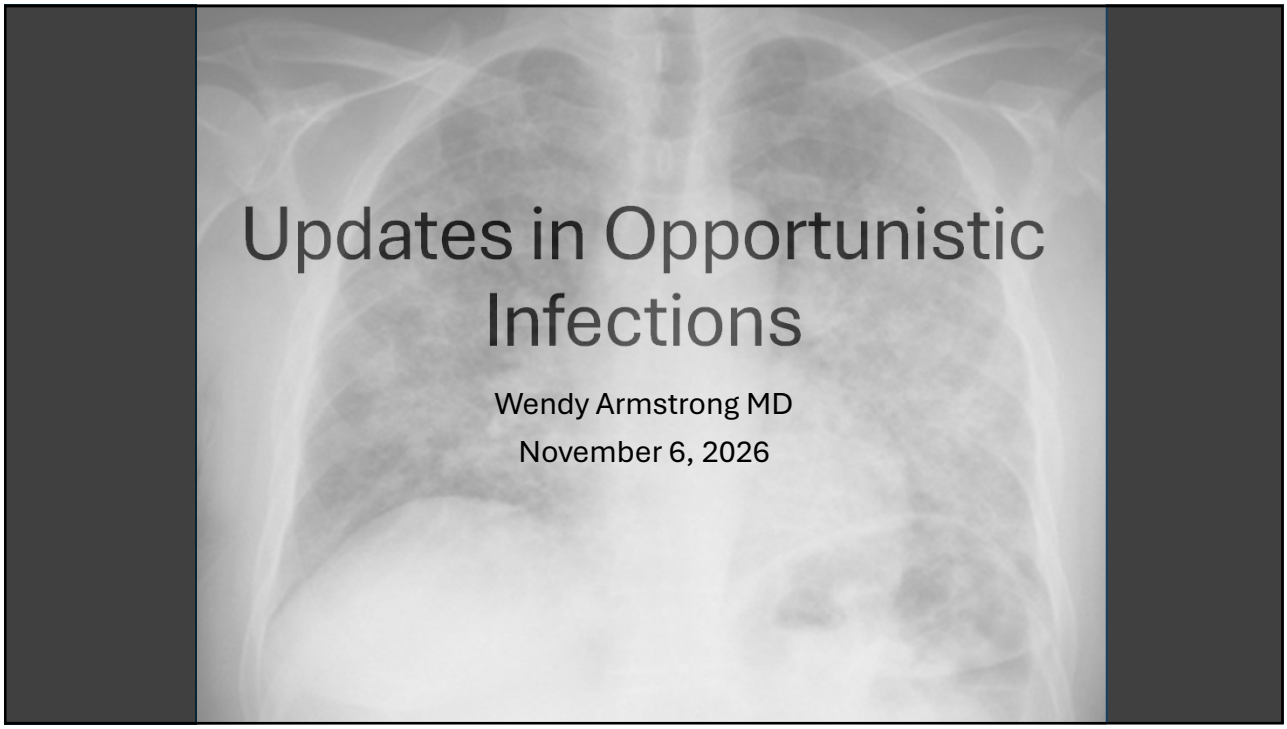


Conflict of Interest

- I have no financial conflicts of interest

Opportunistic infections are seen in a broader range of immunosuppressed states in 2026

↓

Newer presentations, advanced diagnostics, changes in therapy

Pneumocystis Pneumonia
Cryptococcal Meningitis
Toxoplasma Encephalitis

Pneumocystis Pneumonia

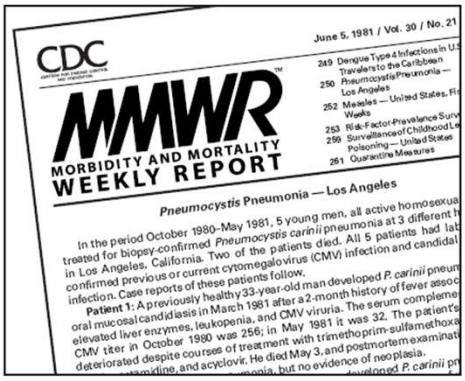
Pneumocystis pneumonia

- Caused by *Pneumocystis jirovecii* in humans (*Pneumocystis carinii* was the rat pathogen)
- Organism cannot be cultured which adds challenge to the diagnosis, determining resistance and basic investigation
- Pulmonary disease is called:

  PCP – **P**neumo**c**ystis **p**neumonia

  PJP – P jirovecii pneumonia
- Treatment and prevention are based on increasingly old data and need to be updated

FIGURE. *MMWR* report on *Pneumocystis* pneumonia in five previously healthy young men in Los Angeles — June 5, 1981



CDC

June 5, 1981 / Vol. 30 / No. 21

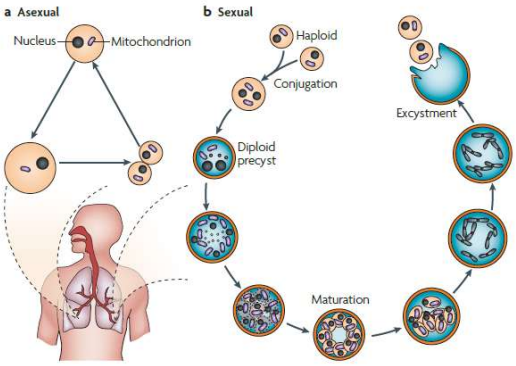
MMWR
MORBIDITY AND MORTALITY WEEKLY REPORT

249 Dengue Type 4 Infections in U.S. Travelers to the Caribbean
250 Pneumocystis Pneumonia — Los Angeles
252 Measles — United States, First Weeks
253 Risk-Factor-Prevalence Surv
259 Surveillance of Childhood Le Poisoning — United States
261 Quarantine Measures

Pneumocystis Pneumonia — Los Angeles

In the period October 1980–May 1981, 5 young men, all active homosexua treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different h in Los Angeles, California. Two of the patients died. All 5 patients had lat confirmed previous or current cytomegalovirus (CMV) infection and candidal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneum oral mucosal candidiasis in March 1981 after a 2-month history of fever assoc elevated liver enzymes, leukopenia, and CMV viruria. The serum compleme CMV titer in October 1980 was 256; in May 1981 it was 32. The patient's deteriorated despite courses of treatment with trimethoprim-sulfamethoxa ...midine, and acyclovir. He died May 3, and postmortem examinat ...monia, but no evidence of neoplasia. ...veloped *P. carinii* pn





CDC Public Health Image Library

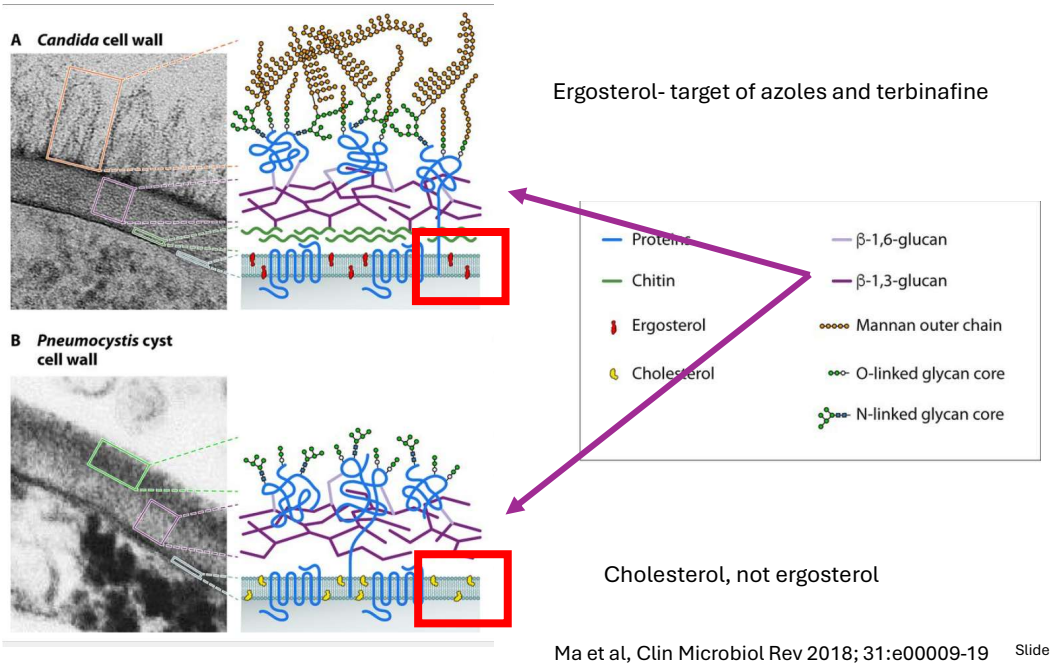
Trophozoite

- Primary form in infection (10:1 trophs: cysts)
- More difficult to detect with staining and small (1-4 microns)

Cyst

- Responsible for transmission (airborne)
- Thick cell wall with beta D glucan (implications for diagnosis and treatment)
- Easily stains and is large (8-10 microns)

Nature Rev Micro, Thomas et al, 2007:5;298



Ergosterol- target of azoles and terbinafine

Cholesterol, not ergosterol

Ma et al, Clin Microbiol Rev 2018; 31:e00009-19

Risk Factors

- CD4+ T cell mediated activation of host macrophages is critical for protection from *Pneumocystis*
- B cells are also critical – the susceptibility to *Pneumocystis* of B cell-deficient mice is similar to that of T cell-deficient mice
- Innate and adaptive immune responses important

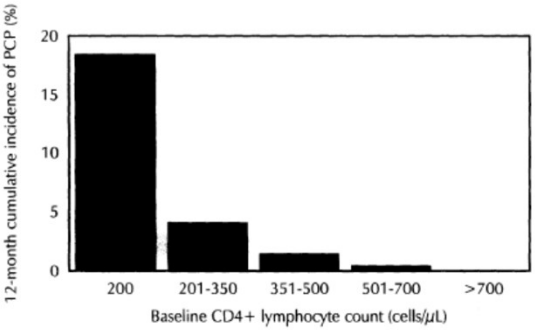


Figure 1. Cumulative incidence of *P. carinii* pneumonia (PCP) among HIV-seropositive men, as related to $CD4^+$ cell count at baseline. Data shown are restricted to those for study participants who were not receiving prophylaxis (adapted from [19]).

Simonds et al, CID 1995:S44-48

Clinical Presentation in PWH

- Systemic
  - Fever, fatigue
- Pulmonary
  - Subacute onset of progressive SOB with DOE
  - Non-productive cough
- Extra-pulmonary disease can occur but is very rare

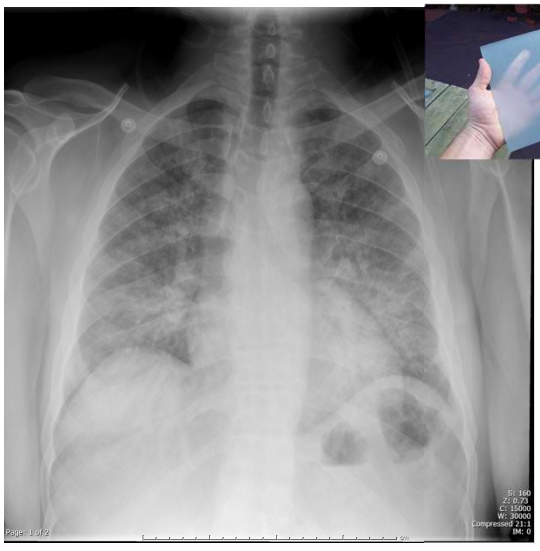
Physical Examination

Other signs that suggest late-stage HIV
- thrush, seb derm, wasting

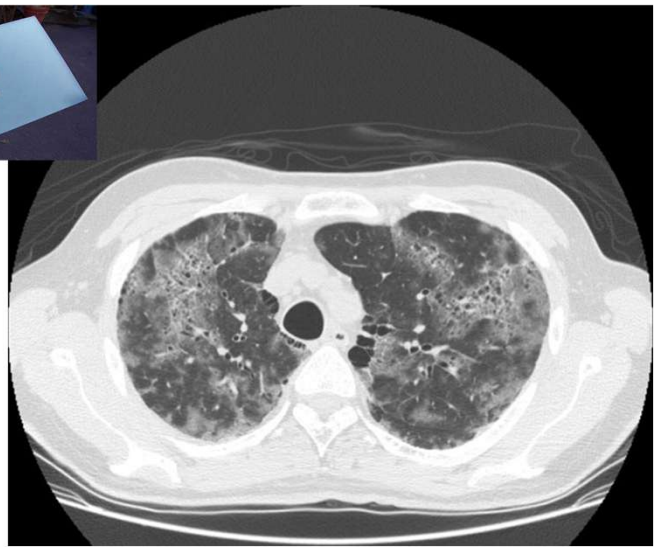
Crackles on examination (may be absent)
Chest pain
Desaturation on ambulatory pulse oximeter testing

PEARL: NP cough plus thrush = PCP until proven otherwise

Imaging: Plain XR and Chest CT



Bilateral interstitial infiltrates is classic
Normal, cystic, nodular, spontaneous PTX



Ground glass infiltrates

Diagnostic Tests

- Serologic
  - LDH
  - Beta-D-glucan
- Respiratory
  - Sources: Induced sputum, BAL, Transbronchial Biopsy
  - Tests: Stain, Immunofluorescence, PCR

Serologic tests

- Lactate Dehydrogenase
  - Poor sensitivity and specificity
  - Reflects lung disease
  - I do not put much stock in this

- Beta-d-glucan testing
  - Great for ruling OUT Pneumocystis pneumonia
  - Many things lead to positive results
  - VERY HIGH in PCP
  - Turn around time is a factor

High sensitivity, lower specificity

Diagnostic Testing: site

Site	Induced Sputum	BAL	TBBX
Pros	*Non-invasive	*Higher specificity and sensitivity than induced sputum	*Can obtain pathology *Very accurate *Will reveal other pathogens
Cons	*Highly dependent on operator *High specificity, lower sensitivity	*Invasive	*Invasive *Unnecessary - adds little to BAL for PCP

Future Directions: Specific serum testing under investigation

Medical Mycology, 2020, 58, 1015–1028

Slide 13

Diagnostic Testing: modality

Test	Cytology	Immunofluorescence	PCR
Pros	*Takes a long time to clear even when on therapy	*Higher sensitivity than cytology, stains trophs and cysts	*Very sensitive *Can be used on other specimen types like NP swabs, trach aspirates
Cons	*Requires expertise *Common stains (GMS, calcofluor white) only stain cysts *Differences in burden affect results	*Differences in burden affect results	*May be overly sensitive *No established cutoff for colonization versus disease

Medical Mycology, 2020, 58, 1015–1028

Slide 14

	Persons with HIV	Persons without HIV
Clinical Presentation	Subacute presentation over weeks	Acute and often more severe
Organism burden	Very high	Lower
Cytology/IF	Easily visualized	Can be more easily missed
PCR	Quantitative values are high	Values lower, may be unclear if colonization
Prophylaxis	Standard recommendations, usually followed	Recommendations are less universally adopted, patients often are not prescribed prophylaxis
Mortality	10 – 30 %	20 - 50%

Slide 15

Expert Opinion on Pharmacotherapy, 22:12, 1579-1592

Treatment of Pneumocystis Pneumonia

First line therapy (mild-moderate-severe)

Trimethoprim/sulfamethoxazole

15 mg/kg IV divided q8h or 2 DS po TID

If severe disease and sulfa allergy – consider desensitization

If mild-moderate disease, can consider second-line agents

Improvement can take 5-7 days. If no improvement, worry about co-infection, IRIS/inflammatory disease, development of fibrotic disease or less likely non-response to TMP/SMX

Treatment of Pneumocystis Pneumonia

- Mild-moderate (not hospitalized)
  - po Atovaquone (if eating and with good absorption)
  - Clindamycin/primaquine (G6PD)
  - Dapsone/trimethoprim (very difficult to obtain, G6PD)
- Moderate-Severe (hospitalized)
  - Clindamycin-primaquine (G6PD)
  - IV pentamidine (only for very severe and cannot desensitize)
- ???? Adjunctive echinocandin in non-response
  - Active only against the cyst form which is not the predominant form
  - Would NEVER use as monotherapy and unclear if it has any role at all

Adjunctive corticosteroids (PWH)

A CONTROLLED TRIAL OF EARLY ADJUNCTIVE TREATMENT WITH CORTICOSTEROIDS FOR *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

NEJM, 1990

For PaO2 < 70 or an Aa gradient >35:

- Prednisone 40 mg bid x 5 days
- Prednisone 40 mg daily x 5 days
- Prednisone 20 mg daily for the duration of therapy (21 days)

Significant decrease in respiratory failure and in death vs no steroids

Increased risk of HSV

Adjunctive corticosteroids (without HIV)

- Studies in mild/moderate disease have not shown benefit.
- Multiple meta-analyses, retrospective and prospective studies have been done. Results have been variable.
- A randomized controlled trial is urgently needed

Open Forum Infect Dis. 2021 Dec; 8(12): ofab545.

Pneumocystis prophylaxis

- First line therapy
  - TMP/SMX DS once daily (also active ppx against Toxoplasmosis)
- Second line therapy
  - TMP/SMX DS TIW
  - TMP/SMX SS daily
  - Dapsone 100 mg daily
  - Atovaquone 1500 once daily
  - Aerosolized pentamidine once/monthly (Respirgard II nebulizer)

The use of IV pentamidine (in HSCT patients once/monthly) is increasing in patients without HIV. Data is more robust in children than adults

Indications for prophylaxis

HIV	CD4 < 200 or CD4% <14
Non-HIV	Prednisone dose >20 mg x 4 weeks
	Lung transplant lifelong, others solid organ transplants are variable
	HSCT usually 6 months unless ongoing immunosuppression
	CAR-T cell recipients for 6 months
	Alemtuzumab, thymoglobulin, ibrutinib (TK inhibitor) and others
	Granulomatous polyangiitis during induction therapy

Discontinuation of primary prophylaxis in persons with HIV: **CD4>200 for > 3 months**
Limited data suggest d/c with CD4>100 and VL suppressed for 3-6 months is acceptable and I do this in certain settings.

Discontinuation of secondary prophylaxis in persons with HIV: attention to CD4 at which Pneumocystis was diagnosed and exercise **more caution** – CD4>200 for > 3 months if Pneumocystis diagnosed at a CD4 < 200.

Guidelines for the Prevention and Treatment of OIs in Adults and Adolescents with HIV

Immune Reconstitution Inflammatory Syndrome and *Pneumocystis* pneumonia

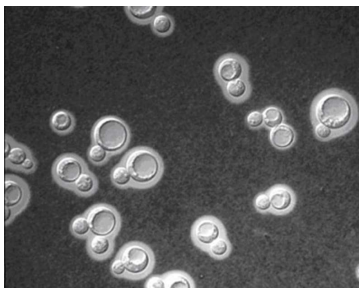
- IRIS has been reported with PCP in the past but is less common than other organisms
- There are some data supporting increased rates of IRIS in the INSTI era but an RCT did not confirm this
- There are no data supporting delaying ART in the setting of PCP, either in the pre-INSTI era or since INSTIs were introduced

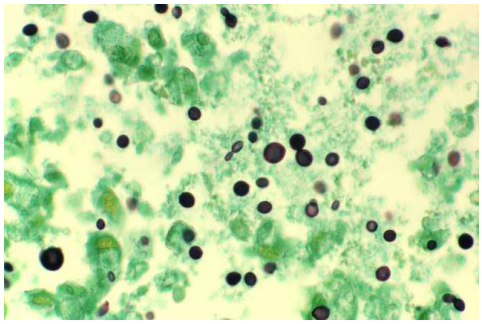
- The best treatment regimens for PCP IRIS are unknown (very high dose steroids, other immunomodulators, standard steroids?)
- The best time to start ART is unknown but for now, would not delay

Cryptococcal disease

Cryptococcus spp

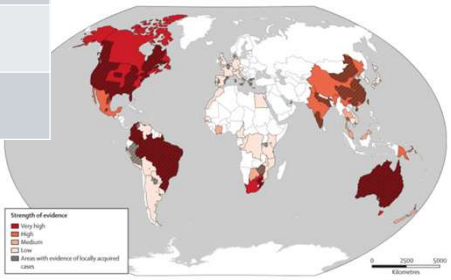
- Encapsulated yeast
- Narrow based budding
- Acquired predominantly by inhalation
- Can have a latent phase with reactivation
  - In phagolysosomes
  - Pulmonary LN complexes, prostate??





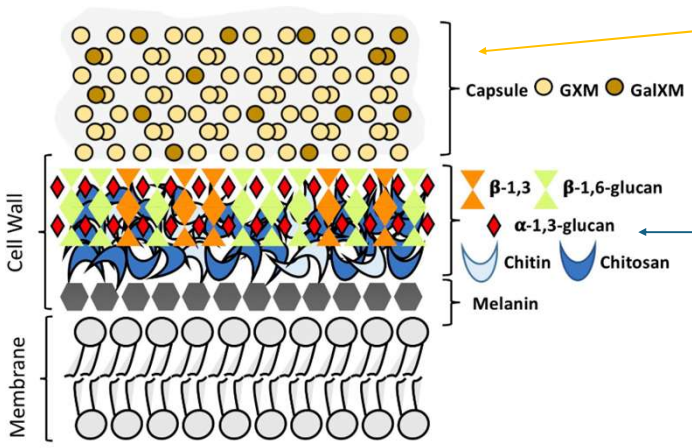
	C. neoformans	C. gattii
Geography	Worldwide	Tropical, subtropical and Pacific NW
Reservoir	Bird excreta, hollows of some trees	Eucalyptus, Firs, Oaks
Host	Predominantly immunocompromised	Immunocompetent and immunocompromised
Growth		Requires CBD media to grow
Virulence	Less virulent	More virulent
Clinical spectrum	Meningitis, pulmonary	More pulmonary disease, cryptococcomas
Treatment		More resistant to azoles

C. gattii



Poplin et al, The Lancet Microbe, 5(12), Dec 2024

The Cryptococcal cell wall



GXM (glucuronyloxolomannan) is the Cryptococcal antigen that our diagnostic tests measure

Abundance of ß-1,6 glucan and α -1,3 glucan >> ß-1,3 glucan renders echinocandins ineffective (and BDG testing negative)

Garcia-Rubio et al, Frontiers in Microbiology https://doi.org/10.3389/fmicb.2019.02993

Risk Factors

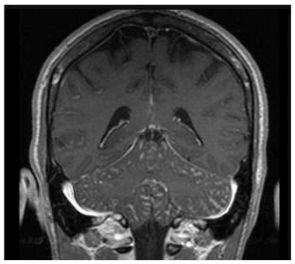
- Disorders of cell-mediated immunity
  - HIV/AIDS (90% have a CD4<100 cells/ml[3])
  - Malignancy, especially heme malignancies
  - Glucocorticoid use, TNF inhibitors
  - Alemtuzumab, thymoglobulin
  - Sarcoidosis
  - Solid organ and stem cell transplantation
  - Cirrhosis
  - And others…..



Clinical Spectrum of Disease

- Pulmonary cryptococcosis
- CNS disease – meningitis and cryptococcomas
- Skin, prostate
- Lymph nodes and reticuloendothelial system
- Can widely disseminate
- Asymptomatic antigenemia





Cryptococcal meningitis

++++ Immune deficits ++



Subacute, often with headache alone
Minimal inflammation – no meningismus
High ICP can lead to CN deficits (hearing, vision)
CSF may have no WBCs
Imaging may show "frozen ventricles"

More acute, fever, HA
Some meningeal irritation
High ICP can lead to CN deficits (hearing, vision)
CSF usually inflammatory
Organism burden is unpredictable, but often lower

Diagnostics

	India Ink	Cryptococcal Antigen Testing	Culture	Pathology
		Latex agglutination Lateral flow assays		
Pros	*Relatively simple	*Qual and Quant testing *Very Rapid (10 min) *LFA now with high sensitivity and specificity (98% for both) *Prognostic value	*Will detect noncapsular Crypto *Gold standard	*Can detect other pathogens *Definitive
Cons	*Almost never done anymore *CSF only *Can be false neg with lower titers	*Misses noncapsular Crypto *Subject to prozone phenomenon *Can be negative in isolated pulmonary disease	*Time	*Invasive

**Biofire panels have a risk of false negatives

Cryptococcal Ag Lateral Flow Assay



Induction -> Maintenance -> Consolidation

	Asx antigenemia	Pulmonary	CNS or non-CNS extrapulmonary disease
Antifungal therapy	LP first HIV: Fluconazole 800 - 1200 mg/day x 2 weeks then 400-800 mg/day x 10 weeks, then 200 mg/day for 6 months	Severe: same as CNS Mild-moderate: Fluconazole 400 mg/day x 6-12 months	LAmB 3-4 mg/kg/day or ABLC 5 mg/kg/day PLUS 5-FC 100 mg/kg/day x 2 weeks THEN Fluconazole 400-800 mg/day x 8 weeks THEN Fluconazole 200-400 mg/day x 6-12 months
Resource limited settings		same	LAmB 10 mg/kg/day x 1 then 5-FC 100 mg/kg/day + Fluconazole 1200mg daily x 2 weeks

Guidelines for the Prevention and Treatment of OIs in Adults and Adolescents with HIV

Elevated Intracranial Pressure: Pearls

- Don't rely on imaging alone!
- Must measure an OP with the LP
- If elevated, no role for steroids, mannitol, acetazolamide
- Serial taps to keep pressure <20
- May need CSF diversion



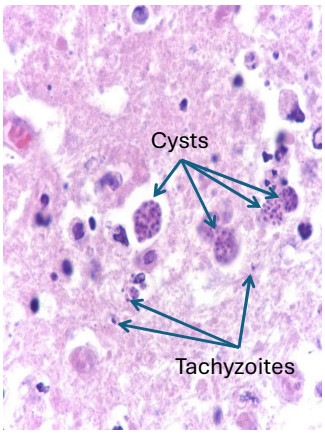
Immune Reconstitution Inflammatory Syndrome (IRIS)

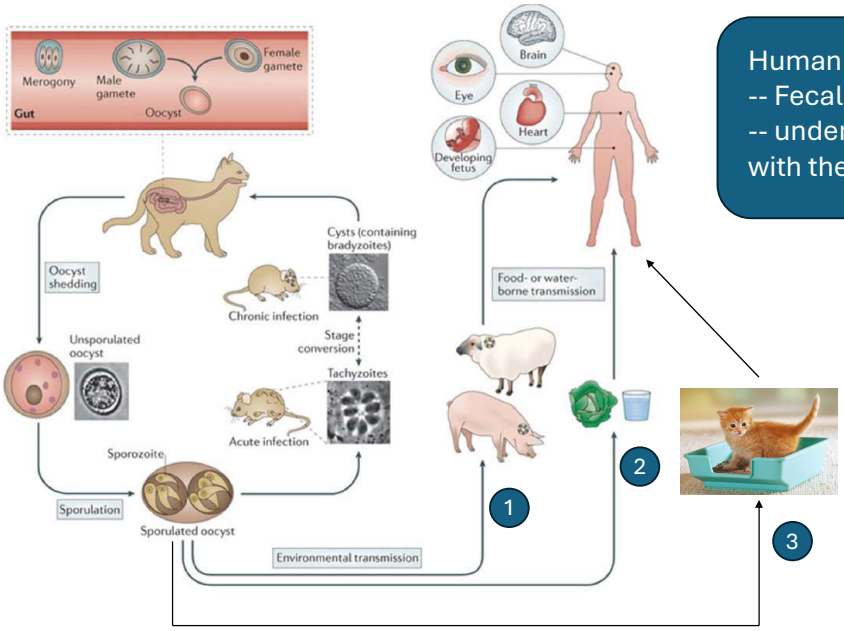
- Recommended to wait 4-6 weeks after initiating anti-fungal therapy to start ART to lower risk of IRIS
- As many as 10-30% of patients with Cryptococcal meningitis can develop IRIS symptoms post starting ART
- Presentation: Increased ICP, increased symptoms
- Very tricky to manage –
  - Relapse vs IRIS
  - Steroids and what is the appropriate dose?
  - ICP and shunt malfunction
- Transplant pts: CAUTION with tapering immunosuppression quickly

Toxoplasma gondii

Toxoplasma gondii

- Protozoa with worldwide distribution
- Definitive host = cats
  (This is where sexual reproduction can happen)
- Intermediate host
  - Cows, pigs, sheep, mice, birds, humans





Human infection comes from:
-- Fecal-oral contamination
-- undercooked meat infected with the tissue phase

Acute Infection

- Asymptomatic
- Mono-like illness with prominent fever, adenopathy, can mimic lymphoma
- Pregnant women can transmit to the fetus - congenital disease
- Seropositivity varies by country, food habits

Reactivation disease

- Toxoplasma encephalitis
- Myocarditis
- Chorioretinitis

In the setting of immune compromise

Risk of Reactivation

HIV	CD4 < 100
Non-HIV	Solid Organ Transplant Recipients
	• D+/R- heart transplant patients at risk of donor-derived myocardial infection
	Sero-positive Hematopoietic Stem Cell Recipients
	High dose Corticosteroids or other immunosuppressants
	Congenital Toxoplasmosis Survivors
	Pregnant women

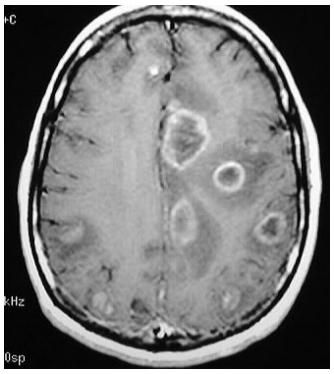
Indications for prophylaxis

HIV	CD4 < 100
Non-HIV	Solid Organ Transplant Recipients
	• D+/R- heart transplant patients at risk of donor-derived myocardial infection
	Sero-positive Hematopoietic Stem Cell Recipients
	High dose Corticosteroids or other immunosuppressants
	Congenital Toxoplasmosis Survivors
	Pregnant women

Prophylaxis: **TMP/SMX DS daily - first line;** DS TIW or SS daily are second line options
Dapsone/pyrimethamine + leucovorin weekly
Atovaquone 1500 mg daily

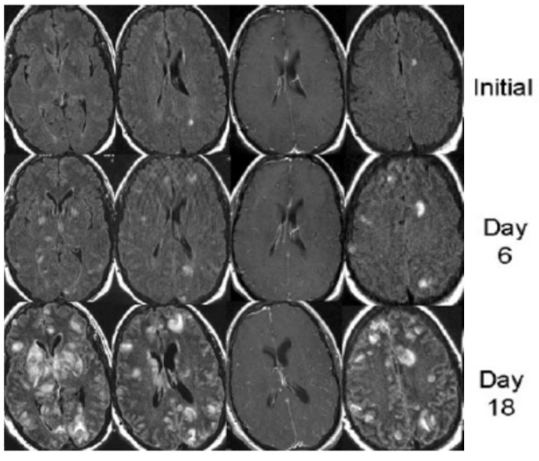
Toxoplasma encephalitis

- Most common presentation is with fever, focal deficits
- Imaging shows multiple ring enhancing lesions in the basal ganglia, thalami and corticomedullary junction associated with edema
- Can be diffuse encephalitis without focal lesions



Transplantation and Toxoplasmosis

- More often acute and widely disseminated
- Occurs in the initial 3-6 months
- Myocarditis in heart transplant pts, also involvement of BM, lungs, CNS and liver
- Progress rapidly to shock in 10%
- Mortality 50% + with disseminated disease



AJNR Am J Neuroradiol 25:270–273, February 2004

Diagnosis

	Toxo IgG	CSF Toxo PCR	Pathology	Treatment Trial
Pros	*Nearly always positive	*Specificity is > 95%	*Definitive	*Non-invasive
Cons	*Sensitive but not specific	*Sensitivity is 50-83%	*Invasive	*Takes time *Delays workup if no response

*Chorioretinitis: EYE exam plus vitreal tap for Toxo PCR (about 70% sensitive/100% specific)
*Congenital disease: PCR of amniotic fluid approaches 100% sensitivity

Initial treatment of Toxoplasma Encephalitis

First-line induction therapies (6+ weeks)

Pyrimethamine + Sulfadiazine + Leukovorin

OR

Trimethoprim/sulfamethoxazole

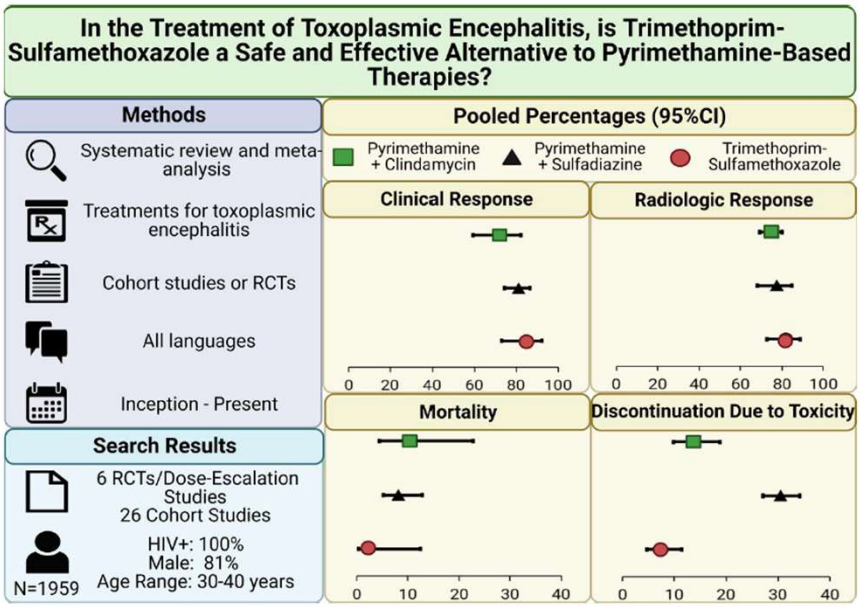
5 mg/kg (TMP component) q12h

Second- and third-line induction therapies

Pyrimethamine + Clindamycin + Leukovorin

High dose Atovaquone

FOLLOWED BY MAINTENANCE THERAPY





New lessons in OI Management

- **Pneumocystis pneumonia:**
  - Beta D glucan is a good exclusionary test if normal
  - PCR is overly sensitive
- **Cryptococcal disease:**
  - Caution with reducing immunosuppression in transplant patients
  - May be a role for single dose LAmB in the future???
- **Toxoplasmosis:**
  - TMP/SMX appears to be a very reasonable alternative to pyrimethamine-based regimens
  - Have a high index of suspicion in transplant patients with unexplained shock