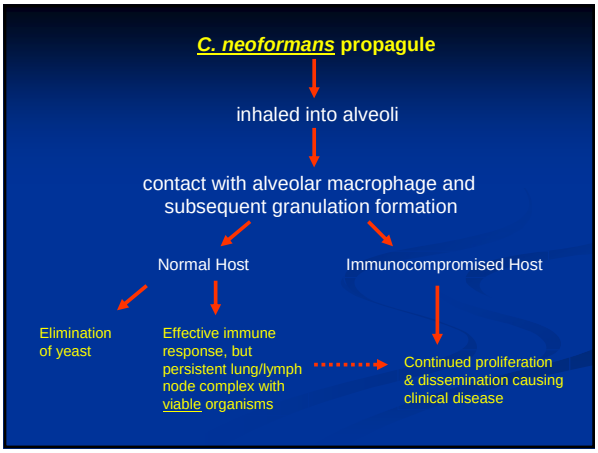
Managing Difficult Cryptococcal Infections and Their Complications

Peter G. Pappas, MD, FACP
Division of Infectious Diseases
University of Alabama at Birmingham

Serotypes of *Crypotococcus*

- *C. neoformans* var. *neoformans* (D)
- *C. neoformans* var. *grubii* (A)
- *C. neoformans* var. *gattii* (B, C)
- *C. neoformans* var. ? (AD)



Epidemiology of *C. neoformans*

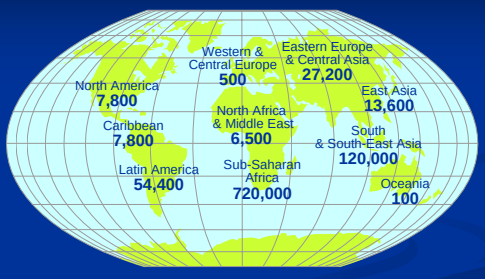
- Worldwide distribution
- Most adults possess antibody to *C. neoformans*
- In NYC, most children have antibody to *C. neoformans* before age 10, although disease is rare prior to late adolescence*.

Goldman et al. Pediatrics 2001; 107:66

Conditions Associated with Cryptococcosis

- HIV infection
- Lymphoproliferative disorders
- Sarcoidosis
- Corticosteroid therapy
- Organ transplantation
- End stage renal disease
- Chronic liver disease
- Hyper-IgM syndrome
- Hyper-IgE syndrome
- Monoclonal antibodies (e.g. infliximab)
- Diabetes mellitus (?)
- No underlying condition (~ 20-25%)

Estimated global cases of HIV-associated cryptococcosis



Global total: 957,900 cases (range: 371,700 – 1,544,000)

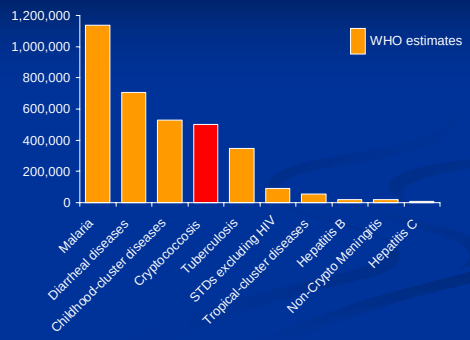
Park et al. AIDS, 2009

Estimated global deaths from HIV-associated cryptococcosis

Global total: 624,700 cases (range: 125,000 – 1,124,900)

Park et al. AIDS, 2009

Estimated deaths in Sub-Saharan Africa from cryptococcosis and other infectious diseases



Case #1

34 yo male with a 6 week h/o progressive headache and confusion. He is homeless, admits to long standing alcoholism, and has a recent h/o injection drug use. No other past medical hx is provided. He is brought to the ED by a companion. The pt c/o modest headache, admits to left gaze diplopia, but denies fever or seizure activity. He reports no other complaints.

Case #1 (cont)

PMH: No additional data, takes no meds.

SH: Homeless, smokes ½ ppd.

PE: Disheveled man, chronically ill appearing. 99.6°, 100/60, 116, 16. O_2 98%.

No rash or LAD. Modest OPC. Chest, CV, abd WNL. No meningismus. Neuro: MMSE 23/30; L 6th CN palsy. No other focal findings.

Routine labs

CBC: WBC 2.3K; PMNs 85%, L 5%, M 4%, B 1%, E 5%; Hgb 8.5; Plt 55K

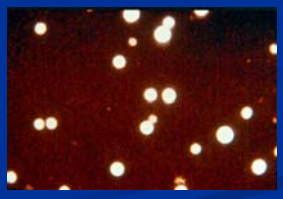
Electrolytes: WNL; Cr 0.8, BUN 12

AST 95, ALT 101, Alk Phos 115, T Bili 1.7, LDH 323 TP 6.8 gms, Alb 3.0

Serology: HCV ab positive; rapid HIV positive; serum CrAg positive

LP Results

OP: 440 mm/CSF, fluid clear
WBCs 12 (100% MNCs)
RBCs 2
Prot 112
Glu 15
CrAg 1:1024
India ink positive
CP: 160 mm/CSF



Hospital Course

Hospital day 1: AmB 0.7 mg/kg plus po 5 FC 100mg/kg in 4 divided doses is initiated.

Hospital day 2: Headache persists. A repeat LP reveals OP of 450 mm/CSF. Initial CSF and blood cultures are positive for yeast, later identified as *C. neoformans*.

Hospital Course

Hospital day 4: Pt has less confusion, but has developed severe nausea and vomiting.

Hospital day 5: Symptoms persist, repeat LP reveals OP >500 mm CSF. Day 2 CSF culture positive for yeast. Serum Cr 1.1

What course of action now?

1. Place VP shunt immediately
2. Stop AmB, begin LFAmB 4-6 mg/kg
3. Stop AmB, begin high dose fluconazole (≥12 mg/kg)
4. Continue frequent LPs (qd or qod) and continue current antifungal therapy
5. Begin voriconazole 4 mg/kg bid

Hospital Course

Nausea and vomiting gradually improve with continued therapy and qod LPs. He still complains of intermittent headache.

Hospital day 14: LP is performed and reveals the following:

OP 250mm/CSF

CrAg 1:256, Protein 90 mg/dl, glucose 25 mg/dl, WBCs 5

India ink positive

A day 10 CSF culture is positive for yeast.

What course of action now?

1. Stop qod LPs, continue AmB plus 5FC
2. Stop LPs and AmB and 5FC, convert to fluconazole 400 mg daily
3. Continue LPs and current therapy until CSF OP < 250 mm CSF and culture is negative, then convert to po fluconazole
4. Continue LPs until OP is consistently < 250 mm CSF, stop AmB and 5FC, convert to po fluconazole

Issues Pertaining to Increased ICP

- Obtain baseline OP
- If OP $\geq$250 mm CSF, then consider reducing by 50% or $\leq$200 mm CSF
- Repeat LPs or lumbar drains for persistently elevated ICP
- Permanent shunting (ie, VP, VA shunts) considered when all other alternatives have failed. Shunts may be placed in the face of active infection if receiving appropriate AFtx.
- Dexamethasone, acetazolamide are not recommended for ICP control.

Perfect JR et al. Clin Infect Dis 2010; 50: 291-322.

Persistent Infection

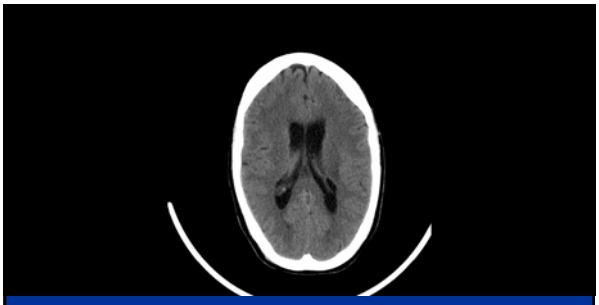
Optimize ART in HIV positive pts (starting within 2-4 weeks from dx)

- Consider increasing AmB from 0.7 to 1.0 mg/kg daily
- Consider adding fluconazole 12 mg/kg/d to AmB if pt is 5FC intolerant
- Generally do not switch to fluconazole monotherapy until CSF cultures are negative.
- Consider susceptibility testing for persistent cases.

Perfect JR et al. Clin Infect Dis 2010; 50: 291-322.

Case #2

39 year old otherwise healthy man presents with HA and low grade fever for 3 months. An LP revealed OP of 340 mm CSF, cultures were positive for *C.neoformans.* A diagnosis of CNS cryptococcosis is made, but despite aggressive therapy with AmB and 5FC for 6 weeks, ICP never normalized, and he required ventriculo-peritoneal shunt. Repeat cultures were negative. Fluconazole was administered for 9 months. He is well 12 months off all antifungals.



Case #2: Ventricular dilatation, no masses noted.

Case #2: lessons learned

- CNS crypto occurs in otherwise 'normal' hosts
- These pts have more subtle presentations, often with sx for *months*
- ICP requiring permanent shunting is often required
- Outcomes are generally no better, and perhaps worse than HIV positive and transplant recipients

Case #3

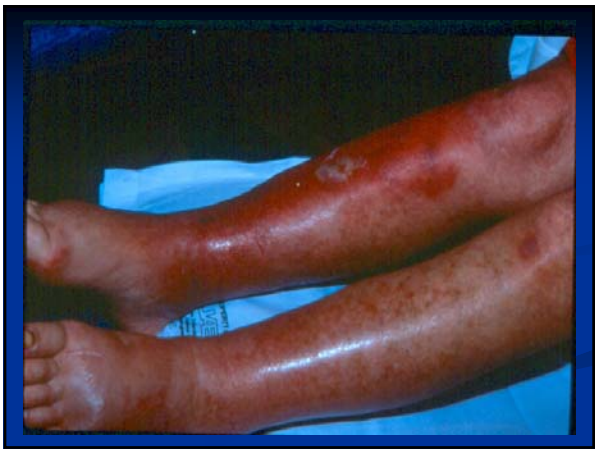
43 yo male underwent cadaveric renal transplantation in 2006. He has had an uncomplicated post-transplant course until 5 days prior to admission, when he developed pain and swelling in both lower extremities, R>L. No h/o trauma, insect bite, etc. No recent rejection history. Current sx preceded by 7 days of low grade fever (99.5°). He has no other complaints.

Case #3 (cont)

PMH: ESRD 2° FSGN, DM, HBP

Immunosuppressives: Prednisone 5 mg/d, tacrolimus 2 mg bid, mycophenylate 500 mg bid.

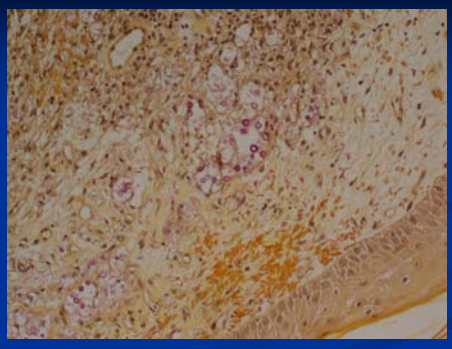
PE: Chronically ill appearing man. 100°, 135/85, 92, 16, O_2 sat 99%. No rash or LAD. Chest, CV, abd WNL. Neuro WNL. Lower extremities notable for bilateral erythema, warmth, and modest 3-4 cm painless shallow ulcer on RLE



Hospital Course

Hospital day 1-3: Nafcillin and ceftazidime initiated empirically with no significant improvement.

Hospital day 4: Skin biopsy performed; 2 BC obtained at admission positive for yeast. LFAmB 5 mg/kg initiated, antibacterials dc'd.



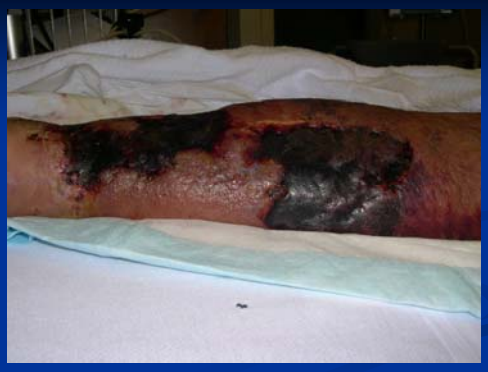
Skin biopsy revealing encapsulated yeasts

Hospital Course

Hospital day 5: mycophenylate dc'd, prednisone decreased to 2.5 mg/d, tacrolimus decreased to 2 mg/d

Hospital days 6-11: mild improvement; BC identified as *C. neoformans.* Serum CrAg 1:512. CSF WNL, CSF CrAg negative.

Hospital day 12: Remains febrile; marked tissue necrosis noted in area of cellulitis.



Baer et al, Transpl Infect Dis

What is the your next step?

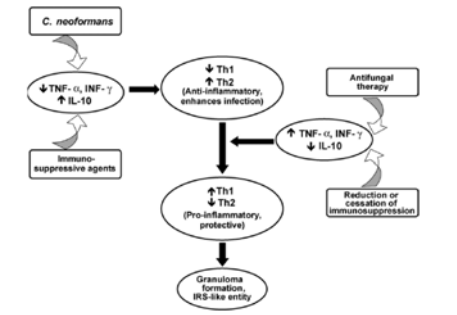
1. Intensify antifungal therapy by adding 5FC
2. Increase LFAmB to 10 mg/kg daily
3. Stop LFAmB and switch to fluconazole
4. Consider slowing the rate of decrease of immunosuppressives
5. Pursue another (additional) diagnosis

Cryptococcal Cellulitis

- Although not unique to transplant recipients, most cases have been described in OTRs.
- Suspect in pts with cellulitis that doesn't respond to conventional antibacterial therapy
- Sites of involvement include bilateral lower extremity, thigh, and upper extremity. Ulcerative lesions are common.
- Diagnosis is simple: skin bx, positive serum CrAg
- Manifestation of IRIS?

Lanternier F et al. Am J Transplant 2007;12:2826(e)

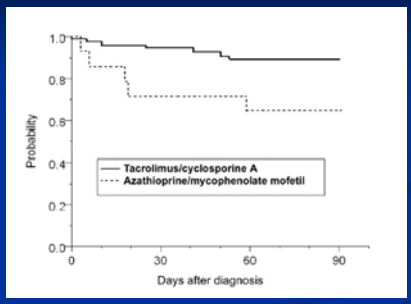
IRIS in Transplant Recipients



Singh N, Lortholary O, Alexander BD. CID 2005, 40:1756-61

Calcineurin Inhibitors and Cryptococcosis

- CIs inhibit growth of *C neoformans* in vitro
- CIs (esp tacrolimus) penetrate CNS, might alter the course of crypto in transplant recipients, resulting in more skin and soft tissue manifestations.
- In vitro data suggests synergy with AmB and fluconazole vs. *C neoformans* strains
- Among OTRs, recent data suggest better survival among CI recipients with crypto



Singh et al JID 2007; 756-64(e)

Case #4

42 year old previously healthy male developed gradual onset of headache and diplopia over duration of four weeks. He lives in Tacoma, WA, and is a salesman traveling throughout the Northwest US including western WA, OR and northern California. He has no significant past medical history. No meds.

Case #4 (cont)

PE: Mildly confused man, no acute distress. 98.9°, 145/92, 64, 14, O_2 sat 100%. Neuro exam notable for L 6th CN palsy, bilateral decreased hearing, no other motor abnormalities. Mild meningismus. Funduscopic exam reveals no papilledema. There is no rash or LAD

Lab: Rapid HIV negative. CBC, electrolytes, LFTs, UA negative. Serum CrAg positive 1:8. CT performed.

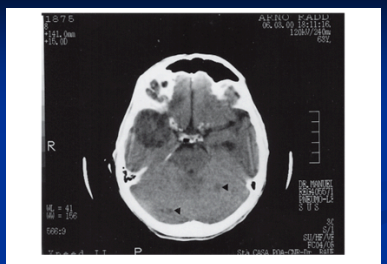


Fig. 2 - Contrast-enhanced axial cranial computed tomographic scan reveals cryptococcoma within the right temporal lobe and multiple nodules (arrows) through the brain parenchyma.

Case #4: Multiple parenchymal lesions, no shift noted.

CSF Findings

OP: 320 mm CSF
Cloudy fluid
WBC: 123 cells/mm^3, 99% lymphs
RBC: 5 cells/mm^3
Protein: 155
Glucose: 19
CrAg: 1:128
India ink negative
CP: 160 mm CSF

Hospital Course

Hospital day 1: LFAmB 5 mg/kg/d and 5FC 100 mg/kg initiated.

Hospital day 2: Pt improved, but HA persists.

Hospital day 5: repeat LP with OP 222 mm CSF. Original CSF culture positive for encapsulated yeast. BC are negative.

Hospital Course

Hospital day 6-27: Slow improvement but persistent L 6th CN palsy. LFAmB plus 5FC continued.

Hospital day 28: repeat CT head scan demonstrates mild improvement from baseline…multiple enhancing lesions, large R temporal lesion unchanged. Day 21 CSF culture is negative

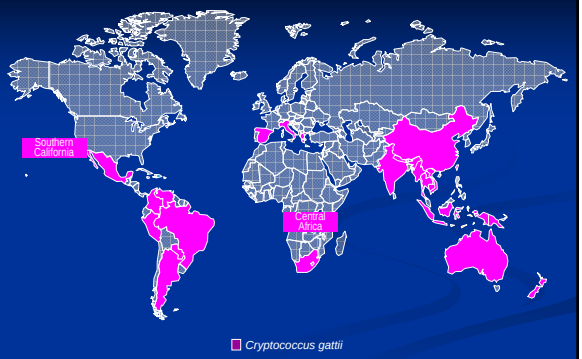
What is your next step?

1. Continue combination therapy with LFAmB plus 5FC as tolerated
2. Switch to po fluconazole 400-800 mg/d
3. Stop therapy..he's already had enough
4. Add interferon gamma to LFAmB and 5FC to enhance immune response.
5. Perform repeat LP to measure OP and obtain culture, base therapy on these results.

Cryptococcus gattii Infection

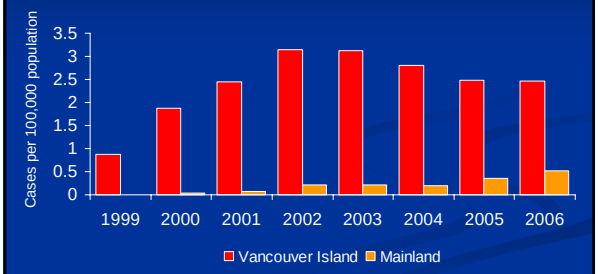
- Traditionally much less common than *C. neoformans*
- Tends to produce disease in otherwise normal hosts
- Tendency to be associated with mass lesions in CNS and lungs
- Persistent infection is typical
- Longer periods of induction and maintenance therapy are usually required.

Geographical distribution of *C gattii*



Incidence of *Cryptococcus gattii* infection British Columbia, Canada

Average incidence 1999–2006:
Vancouver Island: 2.8 cases per 100,000 Mainland: 0.65 cases per 100,000



Source: BC Centre for Disease Control 2007

Cryptococcus gattii in the Pacific Northwestern United States

Cryptococcus gattii: an emerging pathogen?

- Because there is no formal surveillance for *C. gattii* infection in the U.S., cases reported to date represent an under-estimate of the burden of human disease
- Animal cases provide important information regarding the spread of the disease
- Enhanced laboratory testing with routine identification to species level is essential
- Working group with public health and animal health officials from Alaska, California, Idaho, Montana, Oregon, and Washington