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Die Therapie der besonderen Mykose: Kryptokokkose

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Presentation Outline

- Background
- Treatment recommendations of CM
- The continuing role of flucytosine
- Chosing the appropriate polyene
- Managing intracranial pressure
- Recognition and management of IRIS
- Conclusions

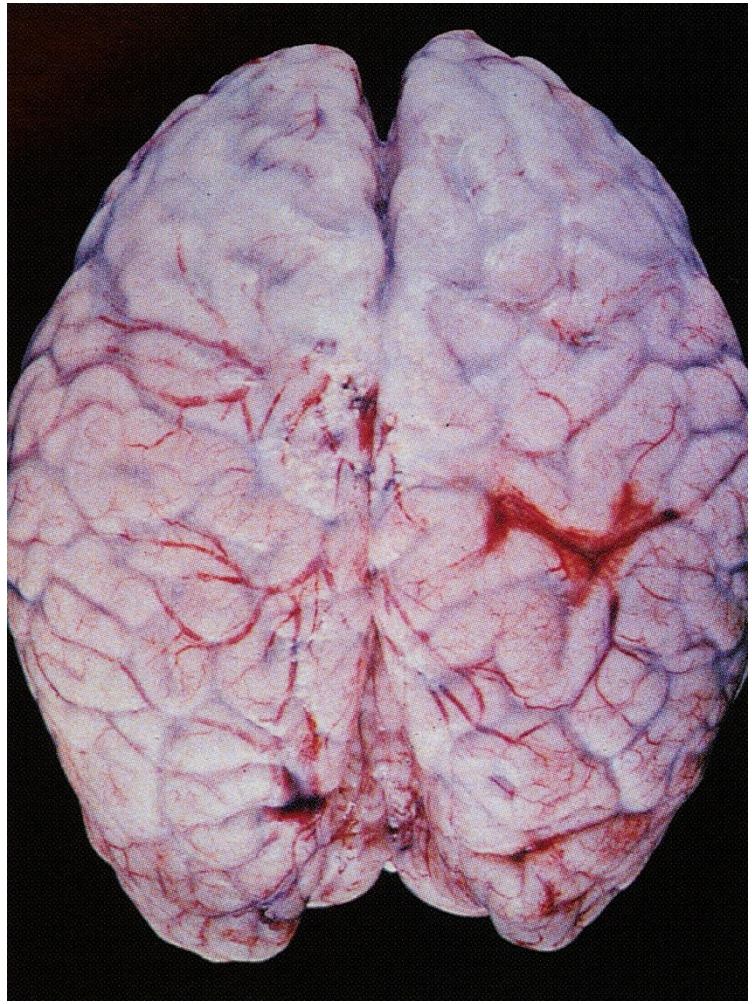
Cryptococcus and Cryptococcal Disease

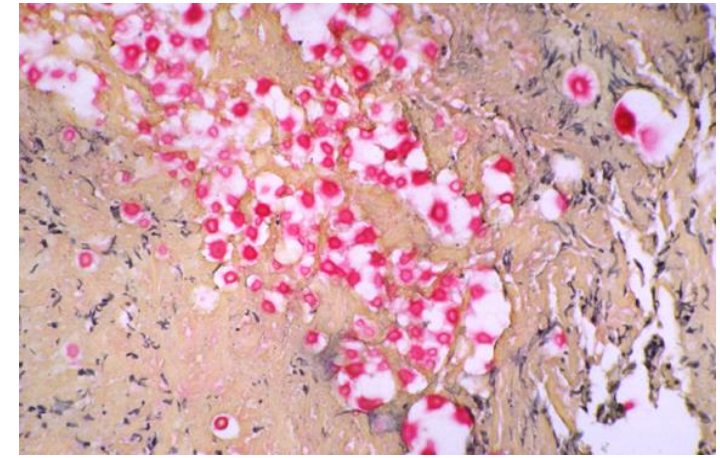
- *Cryptococcus neoformans* / *Cryptococcus gattii*
- Rare *Cryptococcus* spp. (*C.albidus, C.laurentii*…)

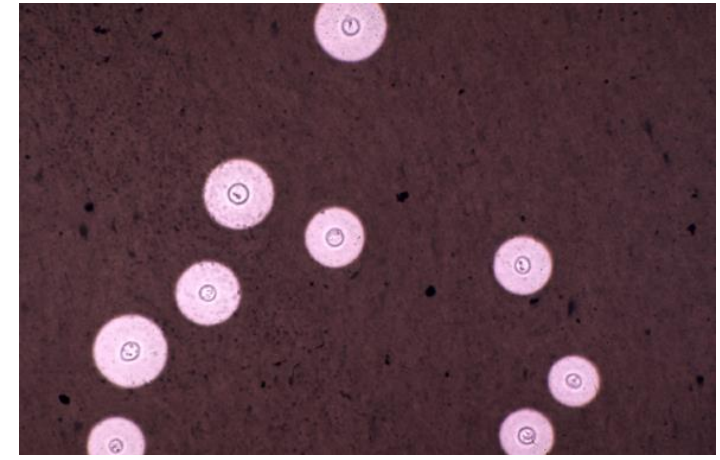
- Opportunistic infection caused by *C.neoformans or C. gattii*, encapsulated yeast, that are neurotrophic

- Clinical diseases associated with *C. neoformans / C. gattii*
  - pulmonary –asymptomatic to mild to progressive, depending on patient and inoculum size
  - CNS: Meningoencephalitis
  - disseminated disease

Cryptococcus and Cryptococcal Disease







Cryptococcus and Cryptococcal Disease

- Associated with defects in T-cell number and -function
  - advanced HIV infection (! Subsaharan Africa, Southeast Asia)
    - global burden of HIV-associated cryptococcosis approximates 1 million cases/year
  - immunosuppressive treatment post transplant
  - treatment with glucocorticosteroids / antibodies
- More rarely in subjects without apparent immunodeficiency
    - *C. gattii* outbreak of cryptococcosis in apparently immunocompetent humans

- *Cryptococcal diseases, risk groups IDSA* [1]
  - *HIV–infected individuals*
  - *Organ transplant recipients*
  - *Non–HIV infected and non-transplant hosts*

Perfect et al. CID 2010

Temporal Trends in Cryptococcosis, Duke UMC, 1996-2009

- Retrospective, single center cohort of 207 patients; 42% HIV-positive, 20% post transplant, 38% HIV-negative/non-transplant

Description	Total		Severe disease (n = 131)[a]						Non-severe disease (n = 76)[a]					
			HIV		Transplant		HIV−/Trans-[b]		HIV		Transplant		HIV−/Trans-[b]	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Attributable death	31	(15)	12	(16)	3	(17)	12	(31)	1	(8)	0	(–)	3	(8)
Overall mortality	52	(25)	15	(20)	5	(28)	16	(41)	2	(17)	1	(4)	13	(33)
IRIS	7	(3)	3	(4)	2	(11)	1	(3)	1	(8)	0	(–)	0	(–)

- 15% attributable mortality, 25% overall through one year of follow-up
- HIV-positive and HIV-negative/non-transplant pts accounted for 89% of attributable deaths and 86% of all-cause mortality in severe disease

Bratton et al. PLOS One 2012

Epidemiology of Cryptococcosis, Germany 2004-2010

- Cryptococcosis not a reportable infectious disease
- Data from Germany accrued by the reference laboratory of the Robert Koch-Institut (RKI) from multiple sources
  - Hospital discharge data, Statistisches Bundesamt
  - Cases of HIV-associated CC reported on a voluntary basis to the RKI
  - Cases submitted by individual laboratories/physicians for identification and or counselling

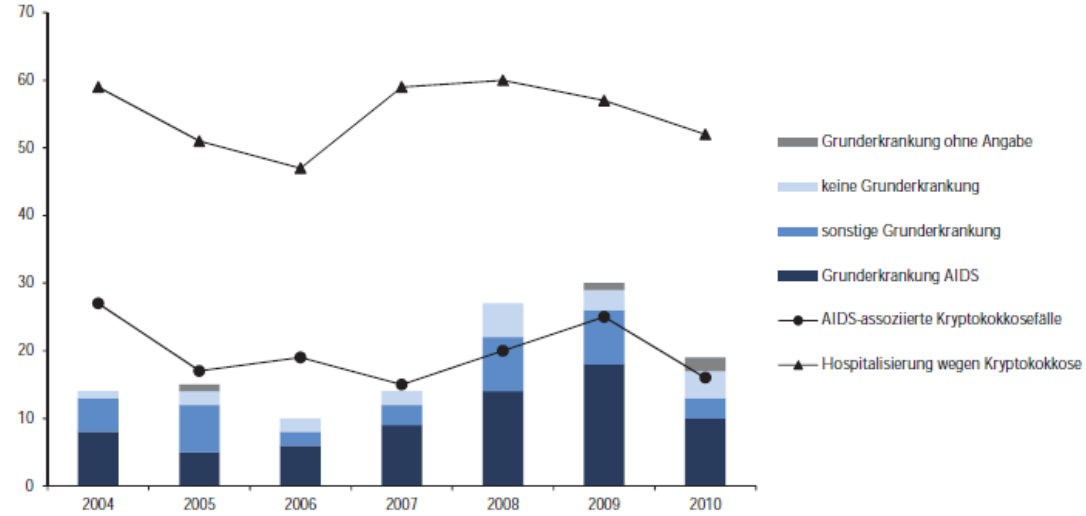


Abb. 1: Zahlen zu Erkrankungen an Kryptokokkose in Deutschland, 2004–2010
▲ Hospitalisationen wegen Kryptokokkose (Statistisches Bundesamt)
● Ärztliche Meldungen von AIDS-assoziierter Kryptokokkose (RKI)
Balken: Im Konsiliarlabor für Kryptokokkose (RKI) dokumentierte Kryptokokkosefälle nach Grunderkrankungen

➢ *Mortality: 9 (HIV) to 20% (all other)*

Rickerts & Tintelnot Epidem Bull 2012

Cryptococcal Disease: IDSA Clinical Practice Guidelines 2010

Key Management Principles of Cryptococcal Meningoencephalitis

- Induction therapy for meningoencephalitis using fungicidal regimens of a polyene and flucytosine, followed by suppressive regimens using fluconazole
- Early recognition and treatment of increased intracranial pressure and/or the Immune Reconstitution Inflammatory Syndrome (IRIS)
- Lipid formulations of AmB in patients with renal impairment
- Correcting and controlling host immunodeficiency and immune reconstitution

Perfect et al. CID 2010

IDSA: HIV-Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	≥1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	≥1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	≥1 year[c]	C-I

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

[a] Begin HAART 2–10 weeks after the start of initial antifungal treatment.

[b] In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made—but not encouraged—as substitutes. See text for dosages.

[c] With successful introduction of HAART, a CD4 cell count ≥100 cells/μL, and low or nondetectable viral load for ≥3 months with minimum of 1 year of antifungal therapy.

[d] Inferior to the primary recommendation.

TDM is recommended for 5-FC with a target 2-h postdose level of 30–80 mg/mL (! < 100 mg/mL)

Perfect et al. CID 2010

IDSA: Organ Transplant Recipients

Regimen	Duration	Evidence
Induction therapy:[a] liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day)[b]	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Immunosuppressive management may require sequential or step-wise reductions.

[b] Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

TDM is recommended for 5-FC with a target 2-h postdose level of 30–80 mg/mL (! < 100 mg/mL)

Perfect et al. CID 2010

IDSA: non-HIV, non-Transplant Patients

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)	≥4 weeks[a,b]	B-II
AmBd (0.7–1.0 mg/kg per day)[c]	≥6 weeks[a,b]	B-II
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) combined with flucytosine, if possible[d]	≥4 weeks[a,b]	B-III
AmBd (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day)[e]	2 weeks	B-II
Consolidation therapy: fluconazole (400–800 mg per day)[f]	8 weeks	B-III
Maintenance therapy: fluconazole (200 mg per day)[b]	6–12 months	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Four weeks are reserved for patients with meningitis who have no neurological complications, who have no significant underlying diseases or immunosuppression, and for whom the cerebrospinal fluid culture performed at the end of 2 weeks of treatment does not yield viable yeasts; during the second 2 weeks, lipid formulations of AmB may be substituted for AmBd.

[b] Fluconazole is given at 200 mg per day to prevent relapse after induction therapy, and consolidation therapy is recommended.

[c] For flucytosine-intolerant patients.

[d] For AmBd-intolerant patients.

[e] For patients who have a low risk of therapeutic failure. Low risk is defined as an early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state, and an excellent clinical response to initial 2-week antifungal combination course.

[f] A higher dosage of fluconazole (800 mg per day) is recommended if the 2-week induction regimen was used and if there is normal renal function.

TDM is recommended for 5-FC with a target 2-h postdose level of 30–80 mg/mL (! < 100 mg/mL)

Perfect et al. CID 2010

IDSA: Monitoring Treatment Responses

- The *2-week lumbar puncture culture result* is test for fungicidal success of induction therapy, and negative cultures at 2 weeks of therapy should be the goal of therapy with AMB plus 5-FC
- Patients who do not reach this goal will need follow-up LPs until the CSF is sterile and consideration to prolong their induction therapy
  - most persistently positive cultures on therapy will grow within 2 weeks
  - CSF culture should represent at least 3–5 mL of fluid
- Value by itself of positive *CSF microscopy* uncertain
- Serial evaluations of *CSF or serum cryptococcal antigen titers* not helpful in the acute management [1,2] may be helpful for late relapses in HIV patients
- New: cryptococcal antigen (CRAG) lateral flow assay (LFA) – high sensitivity/specificity, correlation CN burden, and predictive of early mortality [3]

[1] Perfect et al. CID 2010; [2] Singh et al. CID 2008
[3] Kabanda et al. CID 2013

IDSA: *In vitro* Resistance Testing

- *In vitro* susceptibility testing should be reserved for patients
  - for whom primary therapy has failed
  - who experience relapse after successful primary therapy
  - who develop cryptococcosis and had recent exposure to an antifungal drug
  - live in an area where resistance has been documented

- primary resistance to first-line antifungal drugs is not currently a significant clinical problem
- *In vitro* susceptibility testing (including methods and breakpoints) for *Cryptococcus* species against azoles and AMB not definitively established
- *in vitro* susceptibility testing has not yet been shown to predict early treatment outcome

Perfect et al. CID 2010; Espinel-Ingroff et al. AAC 2012

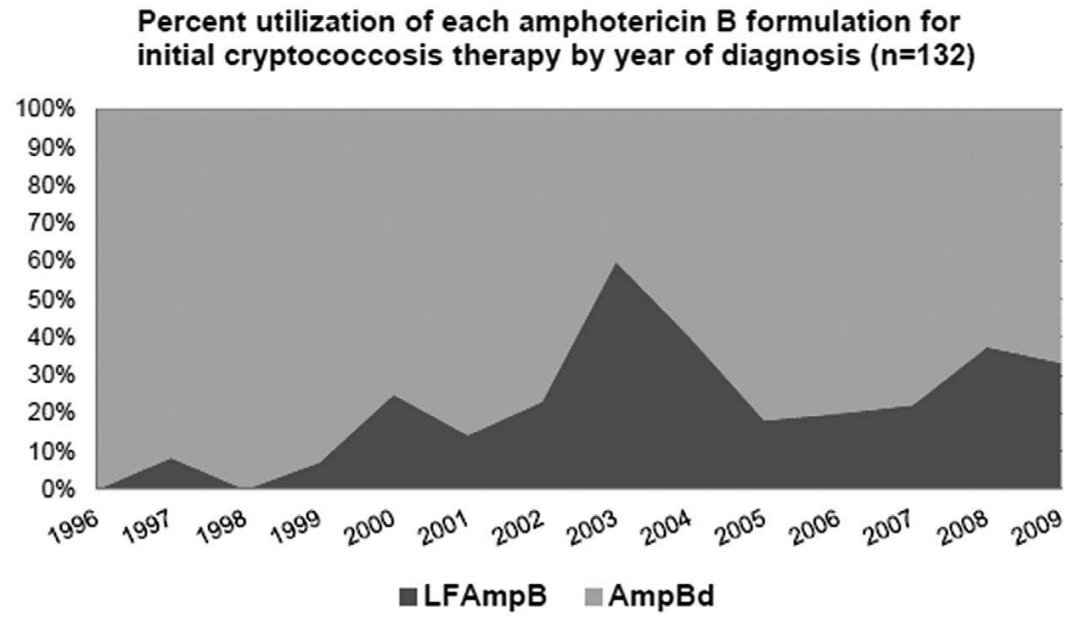
The Continuing Role of Flucytosine

Temporal Trends in Cryptococcosis, Duke UMC, 1996-2009

Initial treatment of cryptococcosis in clinical practice:

Overall 80% of cases with non-severe disease r‘cvd fluconazole for initial therapy

In the severe disease group (CNS, fungemia, dissem.), 87-100% AMB, and 72-83% flucytosine plus AMB with no differences according to disease group



Bratton et al. PLOS One 2012

Temporal Trends in Cryptococcosis, Duke UMC, 1996-2009

Impact of initial antifungal regimen on effectiveness:

- Flucytosine exposure associated with a lower overall (HR, 0.4; 95% CI, 0.2 to 0.9) and attributable mortality rates (HR, 0.5; 95% CI, 0.2 to 1.2)
  - receiving a nonrecommended antifungal regimen associated with a higher relative risk of persistent infection at 4 weeks (RR, 1.9; 95% CI, 0.9 to 4.3)
  - the rate of attributable mortality among those not receiving the recommended dose of initial therapy was higher than in those with recommended dosing (HR, 2.3; 95% CI, 1.0 to 5.0).

- **Supports the 2010 IDSA guidelines as a bestpractice protocol for cryptococcal management**

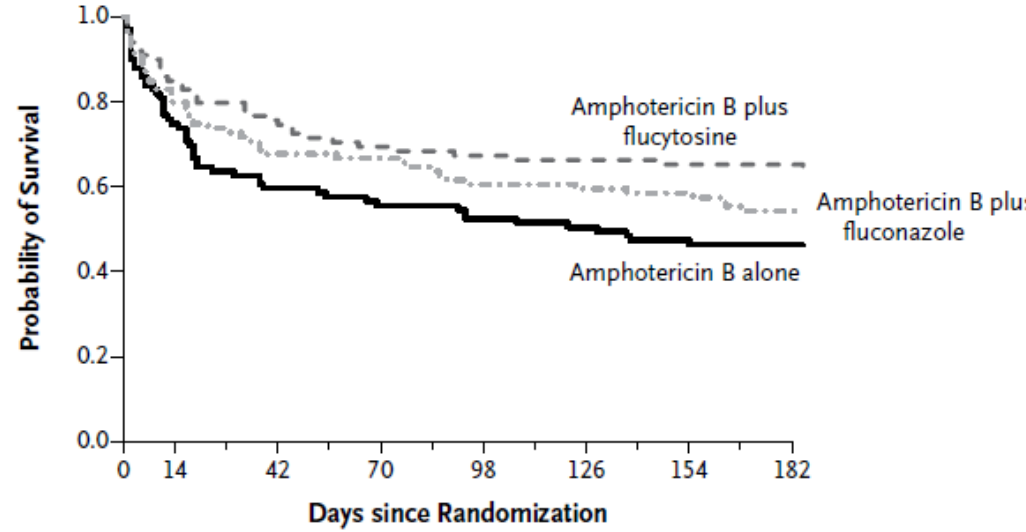
Bratton et al. AAC 2013

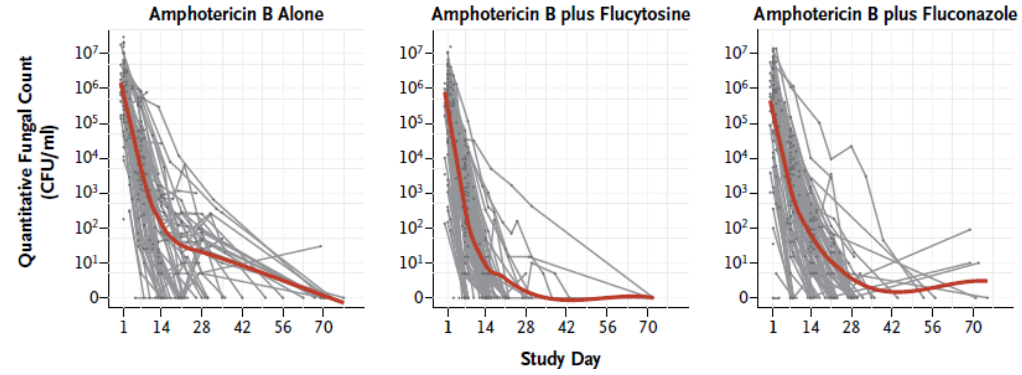
AMB / 5FC Combination for Cryptococcal Meningitis

- Randomized controlled trial in 299 patients

  - 5-FC 100mg/kg + D-AmB 1mg/kg/d x 2 weeks *or*
  - FLU 800mg + D-AmB 1mg/kg/d x 2 weeks

- Endpoint: Survival at 14 and 70 days vs. D-AmB x 4 wks





Day et al. NEJM 2013

AMB / 5FC Combination for Cryptococcal Meningitis

- Three randomized trials provide evidence-based foundation for the combination of D-AmB and 5-FC
- Enhanced killing of yeasts at the site of infection translates into a better outcome
- Benefit of D-AmB and 5-FC is based on in vitro studies, animal models, and further supportive clinical studies

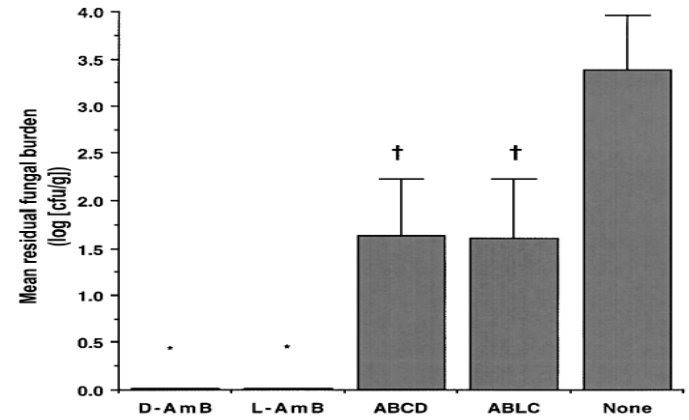
Choosing the appropriate Polyene …

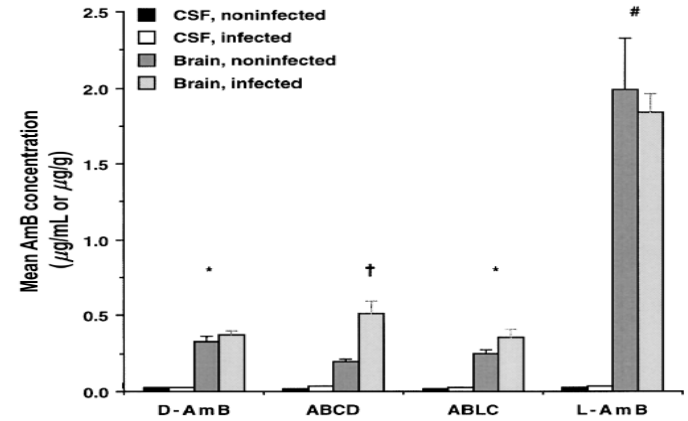
DAMB vs. LAMB for Induction Therapy

- shorter time to CSF sterilization in a very small RCT (*n* = 28) comparing DAMB at 0.7 mg/kg/d with LAMB at 4 mg/kg/day

- no difference in efficacy, but reduced nephrotoxicity in a subsequent larger RCT comparing DAMB at 0.7 mg/kg/day with LAMB at 3 or 6 mg/kg/day found no difference in efficacy

- Neither trial included 5FC as a second drug





Leenders et al. AIDS 1997; Hamill et al. CID 2010; Groll et al. JID 2000

Managing increased Intracranial Pressure

Managing Elevated CSF Pressure

Control of CSF pressure is critical determinant of outcome [1]

- approx. 50% of HIV-infected patients with CM have elevated baseline ICP (> 25 cm H_2O)
- increased ICP linked to high burden of yeast in the CSF

- Early studies suggest association with increased morbidity and mortality [2-4]
  - elevated ICP should be managed aggressively by decompression

- Less data in HIV-negative patients with increased ICP
  - may be more prone to mass lesions / more inflammation

Perfect et al. CID 2010 [1]; Van der Horst et al NEJM 1997 [2]
Graybill et al. CID 2000 [3]; Fessler et al. JAIDS 1998 [4]

Effect of Therapeutic LP's on Acute Mortality

- Among 32 adult HIV-infected inpatients with CM and elevated ICP on ad-mission, *implementation of an ICP management protocol* was associated with a *significant reduction in 30-day mortality (16/35 [46%] vs. 48/64 [75%] in historical controls;* hazard ratio = 2.1 [95% CI: 1.1 to 3.8]; P = 0.018] [1]

- In observational study in 248 individuals with HIV-associated cryptococcal meningitis, *31 deaths (18%) occurred among 173 individuals without a therapeutic LP and 5 deaths (7%) among 75 with at least 1 therapeutic LP*, accounting for a adjusted rel. risk of mortality of 0.31 *(95% C.I. 0.12–0.82)* [2]

  - Therapeutic LPs were associated with a 69% relative improvement in survival, regardless of initial intracranial pressure
  - Individuals receiving therapeutic LPs had higher cerebrospinal fluid (CSF) opening pressures, higher CSF fungal burdens, and were more likely to have altered mental status at baseline than those with no therapeutic LPs

[1] Meda et al. JAIDS 2014; [2] Rolfes et al. CID 2014

IDSA Recommendations: Mgmt. of Elevated CSF Pressure

- *Obtain CSF pressure at baseline*. In the presence of focal neurologic signs or impaired mentation, prior CT- or MRI scan is recommended (B-II)
- If the CSF pressure is ≥25 cm H_2O and there are symptoms of increased intracranial pressure during induction therapy, *relieve by CSF drainage* (by 50% if OP is extremely high or to a normal pressure of 20 cm H_2O) (B-II)
- If there is persistent pressure elevation ≥25 cm H_2O and symptoms, *repeat lumbar puncture daily until the CSF pressure and symptoms have been stabilized for 12 days* and consider temporary percutaneous lumbar drains or ventriculostomy for repeated daily lumbar punctures (B-III)
- Permanent ventriculoperitoneal (VP) shunts should be placed only if the patient is on appropriate antifungal therapy and if more conservative measures have failed. If the patient is receiving an appropriate antifungal regimen, VP shunts can be placed during active infection and without complete sterilization of CNS, if clinically necessary (B-III)

Perfect et al. CID 2010

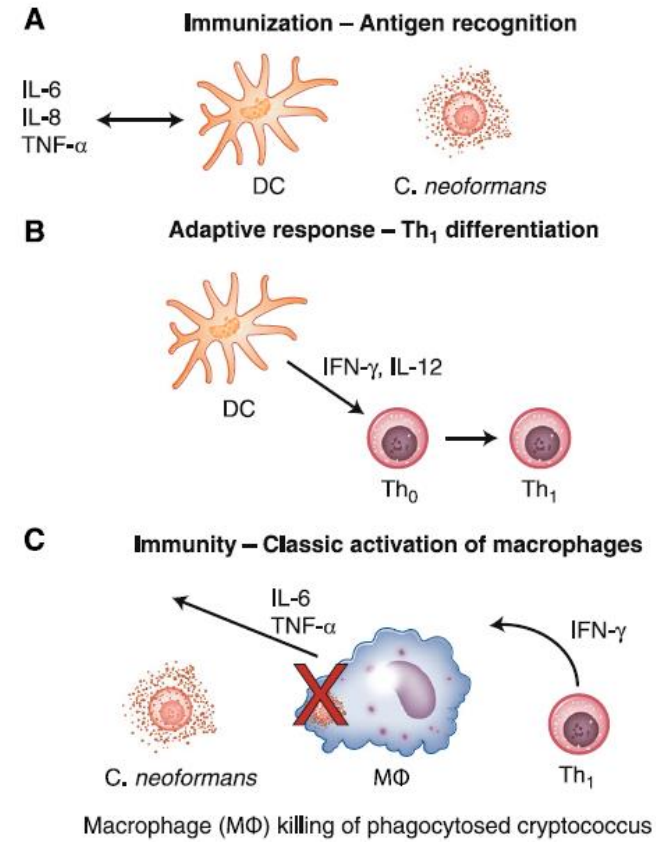
Recognition and Management of IRIS

Managing the Immune Reconstitution Inflammatory Syndrome (IRIS)

Exaggerated inflammatory responses to foreign antigens with (rapid) improvements of the immune system

- common complication of ART in sub-Saharan Africa, particularly with CM
- *also observed in non-HIV immunocompromised patients and 'normal' hosts*

- Risk factors
  - Paucity of CSF inflammation at diagnosis
  - CSF culture positivity at 2 weeks
  - CRP elevation at the time of starting ART
  - *… intensity of immunosuppressive regimen*



Macrophage (MΦ) killing of phagocytosed cryptococcus

Wiesner & Boulware CFIR 2011

Managing the Immune Reconstitution Inflammatory Syndrome (IRIS)

Clinical manifestations compatible with exuberant tissue inflammation in patients with rapid improvement in cellular immunity [1]

- can be lethal if not recognized
- may occur early (within days) or late (weeks to months)
  - as “unmasking” IRIS - *cryptococcal symptoms appear after start of HAART*
  - as “paradoxical” IRIS - *during the treatment and administration of HAART*
- clinical signs and symptoms may include
  - fever with peripheral or mediastinal/abdominal lymphadenitis
  - persistent or recurrent CNS signs and/or symptoms of disease
- no specific laboratory test for detection – clinical diagnosis

Wiesner & Boulware CFIR 2011; Perfect et al. CID 2010

IDSA Recommendations: Recognition and Mgmt. of IRIS

- No need to alter direct antifungal therapy (B-III)
- *No recommendation for minor IRIS manifestations*, as they will resolve spontaneously in days to weeks (B-III)
- *For major complications, such as CNS inflammation with increased ICP, consider corticosteroids (0.5–1.0 mg/kg/d prednisone) and possibly dexamethasone at higher doses for severe CNS signs and symptoms*
  - Length and dose of the corticosteroid taper are empirically chosen according to response, but a 2–6-week course is a reasonable starting point. The course should be given with a concomitant antifungal regimen (B-III)
- Nonsteroidal anti-inflammatory drugs and thalidomide have been used but with too little experience to make a recommendation (C-III).

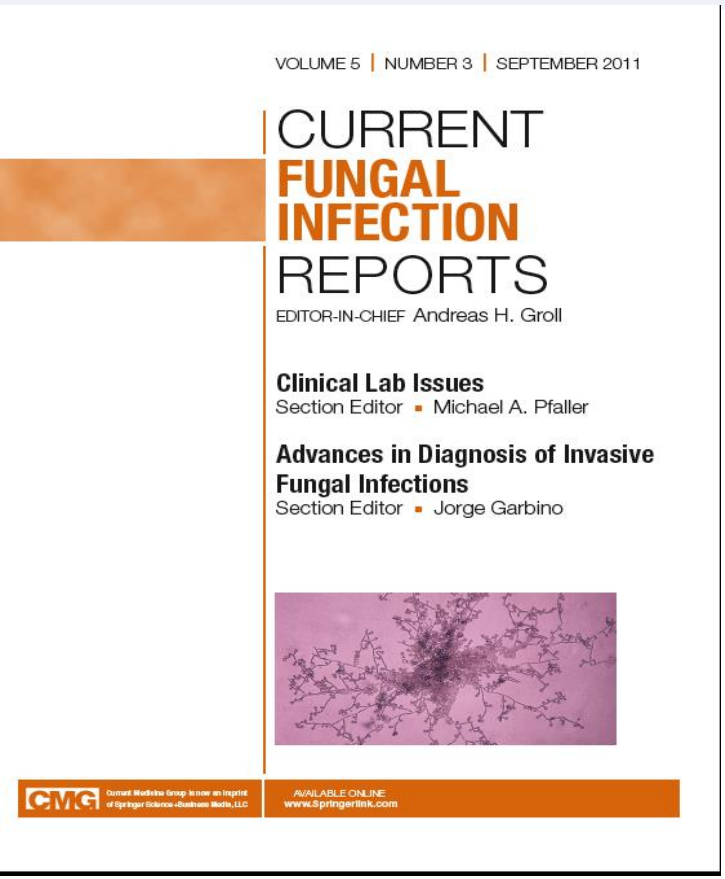
Perfect et al. CID 2010

Conclusions

Key Management Principles

Cryptococcosis remains a challenging management issue

- Induction therapy for meningoencephalitis using fungicidal regimens of a polyene and flucytosine, followed by suppressive regimens using fluconazole
- Early recognition and treatment of increased intracranial pressure and/or IRIS
- Lipid formulations of AmB in patients with renal impairment
- Correcting and controlling host immunodeficiency and immune reconstitution



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IDSA: Cerebral Cryptococcoma

- Induction therapy with DAMB (0.7–1 mg/kg per day IV), LAMB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) *for at least 6 weeks* (B-III)
- Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months (B-III)
- Adjunctive therapies
  - *Corticosteroids* for mass effect / surrounding edema (B-III)
  - *Surgery* for large (3-cm lesion), accessible lesions with mass effect *or* enlarging lesions not explained by IRIS (B-II)

Perfect et al. CID 2010

IDSA: Pulmonary Cryptococcosis

- Meningoencephalitis should be ruled out by L.P. (B-II)
- Pneumonia associated with CNS or dissemination and/or severe pneumonia (ARDS) is treated like CNS disease (B-III)
- For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression and dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III)
- Corticosteroids if ARDS in context of IRIS (B-III)
- Surgery for either diagnosis or persistent radiographic abnormalities / symptoms not responding to therapy (B-III)
- In HIV-infected patients who are receiving HAART with a CD4 cell count ≥100 cells/mL and a cryptococcal antigen titer that is 1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year (B-II)

Perfect et al. CID 2010

Nonmeningeal, Nonpulmonary Cryptococcosis

- For cryptococcemia or dissemination (involvement of at least 2 noncontiguous sites or evidence of high fungal burden based on cryptococcal antigen titer ≥1:512), treat as CNS disease (B-III)
- If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III)

Perfect et al. CID 2010

ESCMID/ECMM: Cryptococcosis caused by Non-*neoformans*, Non-*gattii* Species

- Worldwide prevalence / various environmental sources
- human infection mostly (80%) by *C.albidus, C.laurentii*
- similar presentation (bloodstream > CNS > lung > other sites)
- antigen test often negative and MICs tend to be higher

	Population/ manifestation	Antifungal	Strength of recommendation – quality of evidence	Comments
Cryptococcus other than *C. neoformans* and *C. gattii*	CNS and severe inf. Induction	Amphotericin[a] (±flucytosine[b])	B-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatum* [29,30,33,54–59]
	CNS and severe inf. Consolidation	Fluconazole ≥400 mg/day	C-III	If *in vitro* susceptible
	Non-CNS, not severe inf.	Fluconazole ≥400 mg/day	C-III	MICs of 5-FC, fluconazole and other azoles often elevated and particularly so for *C. albidus*, *C. laurentii* and *C. uniguttulatum* [29,30,33,54–59]
	Non-CNS, not severe inf.	Amphotericin[a]	B-III	May be preferable to fluconazole for the less azole-susceptible species
	Any	Echinocandins	D-II	Intrinsically resistant

Arendrup et al. CMI 2014