Treatment Principles for Candida and Cryptococcus

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The yeasts Candida and Cryptococcus spp. are important human opportunistic pathogens. Candida spp. rely on skin or mucosal breach to cause bloodstream infection, whereas Cryptococcus spp. exploit depressed cell-mediated immunity characteristic of advanced HIV infection. The treatment for both organisms relies on the administration of rapidly fungicidal agents. In candidaemia, source control is important, with removal of prosthetic material and drainage of collections, as well as hunting for and tailoring therapy to disseminated sites of infection, particularly the eyes and heart. For cryptococcal meningitis, restoration of immune function through antiretroviral therapy (ART) is key, together with careful management of the complications of raised intracranial pressure and relapsed infection, both pre- and post-ART.

Candida species (spp.) form part of the normal flora of the human gastrointestinal and genitourinary tracts. Invasive infection occurs in the context of breach of skin or mucosal integrity, often on a background of prior broad-spectrum antibiotic use and defective host innate or cell-mediated immunity. Additional risk factors for candidaemia include diabetes, prolonged intensive care unit stay, presence of a central venous catheter (CVC), recent abdominal surgery, total parenteral nutrition, corticosteroid treatment, and extremes of age (Wey et al. 1989; Saiman et al. 2000; Glockner and Cornely 2013). Additional risk factors in neonates include very low birthweight and necrotizing enterocolitis (Farmaki et al. 2007; Filioti et al. 2007).

As the population of susceptible individuals rises, the incidence of invasive candidiasis is increasing (Pfaller and Diekema 2012), with Candida (spp.) now the fourth most common cause of nosocomial bloodstream infection (BSI) in the United States (8%–10% of all nosocomial BSIs) (Wisplinghoff et al. 2004), with similar prevalence reported in Europe (Engel et al. 2007; Vincent et al. 2009). Treatment is with an antifungal agent from the azole, polyene (amphotericin B), or echinocandin drug classes. With widespread use of azoles for prophylaxis and treatment, there has been a shift in epidemiology from Candida albicans to non-albicans species. Recently acquired resistance to echinocandins has also been reported (Alexander et al. 2013). Source control is important,
and hematogenous dissemination of Candida can result in seeding and distant foci of infection, requiring specific modification of antifungal therapy.

The following five principles summarize the most important aspects of the management of invasive candidiasis.

**PRINCIPLE 1: ADMINISTER AN AGENT LIKELY TO CLEAR Candida RAPIDLY AND EFFECTIVELY**

Early, effective, and rapidly fungicidal treatment is essential given that invasive candidiasis has an attributable mortality rate up to 50% (Gudlaugsson et al. 2003; Zaoutis et al. 2005), and mortality is directly correlated with delays in initiation of adequate antifungal therapy (Morrill et al. 2005; Garey et al. 2006).

Local epidemiology should guide empiric management with both the prevalence of different Candida spp. and the rate of fluconazole-resistance being important considerations. For instance, prior azole use in an individual patient is a risk factor for an azole-resistant infection (Bassett et al. 2010).

Because of their efficacy, spectrum, and safety, echinocandins are preferred empirically in hemodynamically unstable and/or neutropenic patients, those with prior azole use, in known non-albicans species, or empirically in centers with high prevalence of non-albicans species (particularly Candida glabrata) or fluconazole resistance. Fluconazole is favored for clinically stable, immunocompetent patients, those with known susceptible isolates, and in centers with a high prevalence of Candida parapsilosis (which has higher MICs to echinocandins) or low azole resistance (Pappas et al. 2009a). To date, there is no evidence to suggest superior efficacy of any particular echinocandin, nor in favor of combination therapy for invasive candidiasis (Table 1).

The site of infection, renal and hepatic function, concomitant interacting medicines, specific contraindications, and the adverse reaction profile for individual patients should be taken into consideration.

**PRINCIPLE 2: LOOK FOR THE SOURCE AND REMOVE IT WHERE POSSIBLE**

Source control is critical in the management of invasive candidiasis. Infected devices should be removed and collections drained wherever possible. Failure to achieve timely source control is associated with mortality in patients with septic shock (Kollef et al. 2012).

The impact of CVC removal on mortality is controversial. Quantitation of cultures taken from the line versus peripherally can help identify catheter-associated candidaemia and prioritization for removal in patients with tunneled lines (Raad et al. 2004).

Candida spp. readily form biofilms on invasive devices (intravenous lines, catheters, prosthetic heart valves, stents, prosthetic joints), contributing to difficulties in clearance of infection because of their higher resistance to both antifungal drugs and host immune responses (Table 2) (Ramage et al. 2005). Activity against biofilm is important particularly when optimal source control is not achievable, and varies among different antifungal agents. In particular, azoles are not active against sessile forms of Candida spp., whereas echinocandins and amphotericin B have both fungicidal activity and good penetration into biofilms on vascular devices (Bassett et al. 2010; Ruhnke et al. 2011).

**PRINCIPLE 3: MODIFY EMPIRIC THERAPY ACCORDING TO SPECIES DETERMINATION AND SUSCEPTIBILITY TESTING**

For stable patients with fluconazole-susceptible strains, de-escalation to fluconazole should be considered. Patients who have improved clinically and who have cleared Candida from the bloodstream might be suitable for step-down oral therapy to complete the course. Available oral options include fluconazole, itraconazole, voriconazole, and posaconazole. Fluconazole is preferred for susceptible species, whereas voriconazole may be indicated as step-down therapy for Candida krusei or voriconazole-susceptible C. glabrata (Pappas et al. 2009a).
PRINCIPLE 4: CONFIRM CLEARANCE OF Candida

Treatment efficacy should be assessed by documentation of blood culture sterilization, and treatment continued for 14 d after clearance of Candida, providing there is no evidence of disseminated infection (Pappas et al. 2009a). Other modifiable factors driving persistence of infection should also be addressed. If clinically feasible, immunosuppressive and antibacterial therapy should be reduced/de-escalated or stopped (Labelle et al. 2008) and glycemic control in diabetics optimized.

PRINCIPLE 5: CHECK FOR DISSEMINATED INFECTION AND TREAT ACCORDINGLY

Although invasive candidiasis is commonly limited to the bloodstream, organ involvement following hematogenous dissemination is an important manifestation of the disease and may involve the kidneys, myocardium, liver, spleen, bone, central nervous system (CNS), or eyes (Schwesinger et al. 2005; Thorn et al. 2010). Persistent candidaemia is an important risk factor for disseminated infection (Meister et al. 1977; Donhuijsen et al. 1991; Zaoutis et al. 2004; Masood and Sallah 2005). Symptoms and signs are determined by the type and extent of organ involvement.

Fundoscopy is warranted in all patients to exclude endophthalmitis. Endocarditis should be excluded in diagnosis of cases of persistent candidaemia, known valvular pathology, or any other symptom or sign suggestive of endocardial involvement (Pappas et al. 2009a).

EYE

The reported incidence of Candida endophthalmitis or chorioretinitis in patients with candidaemia ranges between 5% and 78% (Raoult 2011), with most recent studies reporting an incidence in the lower end of this range (Donhue et al. 1994; Benjamin et al. 2003; Rodriguez-Adrián et al. 2003). Antifungal therapy of Candida chorioretinitis is similar to candidaemia, but treatment should be continued for at least 4–6 wk until the resolution of all symptoms and signs (Pappas et al. 2009a).

Therapeutic options in Candida endophthalmitis include amphotericin B, fluconazole, and voriconazole. Owing to excellent penetration into the eye, the addition of flucytosine is suggested by some sources. Failures have been reported with echinocandin therapy, attributable to low tissue penetration (Breit et al. 2005; Gauthier et al. 2005; Sarria et al. 2005). Case reports suggest that patients with decreased visual acuity may benefit from early vitrectomy combined with intravitreal instillation of amphotericin B (Essman et al. 1997; Martínez-Vázquez et al. 1998; Khan et al. 2007).

RENAL TRACT

Removal or exchange of foreign bodies in the renal tract (catheters and stents) is an important...
**Table 2.** Antifungal classes, agents, spectrum, and dosing in the treatment of invasive candidiasis

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug</th>
<th>Amphotericin B deoxycholate</th>
<th>Liposomal AmB</th>
<th>Lipid complex AmB</th>
<th>Anidulafungin</th>
<th>Caspofungin</th>
<th>Micafungin</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
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<td>C. albicans</td>
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<tr>
<td>C. glabrata</td>
<td></td>
<td>S</td>
<td></td>
<td></td>
<td>S</td>
<td></td>
<td></td>
<td>S to R</td>
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<tr>
<td>C. krusei</td>
<td></td>
<td>S</td>
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<td></td>
<td>S</td>
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<td></td>
<td>R</td>
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<tr>
<td>C. lusitaniae</td>
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<td>S to R</td>
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<tr>
<td>C. parapsilosis</td>
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<td>S to R</td>
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<td>C. tropicalis</td>
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<td><strong>Available formulations</strong></td>
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<td>IV</td>
<td>Oral</td>
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<tr>
<td><strong>Dosing for treatment of candidaemia</strong></td>
<td></td>
<td>Loading dose (first 24 h) in adults</td>
<td>200 mg</td>
<td>70 mg</td>
<td>–</td>
<td>12 mg/kg</td>
<td>6 mg/kg (12 hourly)</td>
<td></td>
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<tr>
<td>Maintenance dose in adults</td>
<td>0.5–1 mg/kg</td>
<td>3 mg/kg</td>
<td>5 mg/kg</td>
<td>100 mg</td>
<td>50 mg (if &gt;85 kg)</td>
<td>100 mg</td>
<td>6 mg/kg</td>
<td>3 mg/kg (12 hourly)</td>
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<tr>
<td>Dose adjustment in renal impairment</td>
<td>Contraindicated</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Reduce dose</td>
<td>Avoid IV formulation</td>
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<tr>
<td>Dose adjustment in moderate hepatic impairment</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>None</td>
<td>Dose reduce</td>
<td>None</td>
<td>Reduce maintenance dose</td>
<td>Halve maintenance dose</td>
<td></td>
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<tr>
<td>Dose adjustment in severe hepatic impairment</td>
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<td>Unknown</td>
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AmB, amphotericin B; S, susceptible; S-DD, susceptible dose dependent; R, resistant.

aspect of managing invasive candidiasis with a urinary focus (Pappas et al. 2009a). If urine cultures persistently grow *Candida* spp., an ultrasound should be performed to exclude possible renal parenchyma infection. Fluconazole and amphotericin B are effective options for infections in the renal tract (Pappas et al. 2009a) with addition of flucytosine, which is renally excreted, sometimes recommended in complicated infections or infections caused by non-*albicans* species (Ruhnke et al. 2011). Neither echinocandins nor voriconazole reach adequate levels in the urine, making them less suitable for treatment of infections involving the lower urinary tract (Deresinski and Stevens 2003; Johnson and Kauffman 2003; Chandrasekar and Sobel 2006; Vazquez and Sobel 2006). Conventional amphotericin may be preferred to lipid formulations because of greater penetration into the renal tract (Pappas et al. 2009a), but its nephrotoxicity can be a problem.

**BONE**

Bone infection occurs via either hematogenous seeding or exogenous inoculation (e.g., during surgery). Debridement and removal of any prostheses, in addition to systemic antifungal treatment for 6–12 mo, is recommended. If prostatic material is retained, an agent with good biofilm penetration may be preferable (Ruhnke et al. 2011).

**ENDOCARDIUM**

*Candida* endocarditis is a rare but serious complication (Baddley et al. 2008) and should be excluded by repeated negative blood cultures and a prompt transesophageal echocardiogram wherever suspected (Mylonakis and Calderwood 2001; Pierrotti and Baddour 2002; Tleyjeh et al. 2007). Therapy includes surgical removal of the infected tissue in combination with prolonged antifungal therapy (Steinbach et al. 2005; Salamon et al. 2007; Baddley et al. 2008). Most published guidelines suggest amphotericin B combined with flucytosine for at least 6 wk following valve surgery (Ellis et al. 2001; Pierrotti and Baddour 2002). However, echinocandin therapy is gaining interest because of its superior in vitro activity against biofilms and is recommended as first-line therapy in the more recently published British endocarditis guidelines (Gould et al. 2012). Higher doses may be necessary than those licensed for treatment of candidaemia. Fluconazole is appropriate consolidation therapy for patients with native valve endocarditis, infections caused by *C. parapsilosis*, and as long-term suppressive therapy in which removal of the prosthetic valve is not possible (Gould et al. 2012).

**CNS**

Combination of amphotericin B and flucytosine has been advocated for CNS infections, owing to the rapid fungicidal activity of the former, the excellent CNS penetration of the latter and their documented synergistic activity and the clinical efficacy in *Candida* and cryptococcal infections (Vermes et al. 2000). Alternative options include fluconazole, alone or in combination with flucytosine, particularly for consolidation therapy, and voriconazole, which shows good levels in the CNS (Lutsar et al. 2003) and promising data in patients with CNS aspergillosis (Schwartz et al. 2005). Echinocandin monotherapy is not recommended as penetration into the CNS may be insufficient (Raoult 2011). Antifungal therapy for CNS candidiasis is recommended for at least 4 wk after the resolution of all signs and symptoms of the infection. Removal of any prosthetic material (e.g., drains or shunts) associated with the infection is indicated. Brain abscesses may require neurosurgical drainage (Pappas et al. 2009a).

**CRYPTOCOCCOSIS**

Cryptococcosis is an infection caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. The organism is inhaled into the lungs, where infection may be asymptomatic and resolve spontaneously or present clinically as pneumonia with subsequent hematogenous dissemination to other organs. Disseminated infection is more common in immunocompromised hosts, usually owing
to either HIV infection (Jarvis and Harrison 2007) or iatrogenic immunosuppression following transplantation (Snydman et al. 2008), and may occur following years of latent infection (Garcia-Hermoso et al. 1999; Saha et al. 2007). The central nervous system is the most common site of disease after the lungs, with meningoencephalitis manifesting as headache, meningism, and altered mental status, complicated by seizures and raised intracranial pressure. Focal lesions (cryptococcomas in lung and brain) are more common in C. gattii disease in the immunocompetent host (Mitchell et al. 1995).

Globally, the most common manifestation of cryptococcosis is as cryptococcal meningoencephalitis (CM) in patients with advanced HIV infection and CD4 counts <100 cells/μL. Our antifungal armamentarium against cryptococcosis consists of three drugs: amphotericin B deoxycholate, AmBd (and its liposomal derivatives), flucytosine (5FC), and fluconazole. Despite having one of the most extensively evidence-based treatments among invasive mycoses, acute (10-wk) mortality in CM in HIV remains unacceptably high, ranging from 10%–50% in published cohort and clinical trials, depending on the clinical setting (Perfect et al. 2010).

The management of cryptococcosis is based around seven principles.

**Risk Stratification**

Patients should be assessed for evidence of dissemination and markers of disease severity at presentation. Patients with mild to moderate pneumonia can be treated with fluconazole 400 mg/d, whereas patients with severe pneumonia (ARDS) or evidence of extrapulmonary dissemination need intravenous AmBd with flucytosine (dosed as for CNS disease; Table 1) for 2 wk followed by fluconazole for 6–12 mo (Perfect et al. 2010).

For HIV-associated CM, established adverse prognostic markers are high baseline fungal burden (using either quantitative cerebrospinal fluid [CSF] cultures or cryptococcal antigen titer) and altered mental status (Glasgow coma scale [GCS] <15 and/or seizures) at presentation (Bicanic et al. 2009). These patients may require longer duration of treatment to sterilize the CSF and more aggressive management of ICP, and are more likely to develop CM-immune reconstitution inflammatory syndrome (IRIS) following initiation of ART (Bicanic et al. 2009a; Boulware et al. 2010; Jarvis et al. 2012).

**Clear the Fungus Rapidly**

CM treatment can be divided into three phases: induction, consolidation, and maintenance (Table 1) (Perfect et al. 2010). The rate of clearance of cryptococci from the CSF has been shown to be independently associated with both 2- and 10-wk mortality (Bicanic et al. 2009c). The use of the most rapidly fungicidal combinations in the induction phase of treatment (at least 2 wk, and longer in the immunocompetent host and/or C gattii infection) is thus recommended for any patient with CNS disease. The combination of AmBd (0.7–1.0 mg/kg/d) and 5FC (25 mg/kg four times a day) sterilizes the CSF most rapidly (van der Horst et al. 1997; Brouwer et al. 2004; Day et al. 2013), and showed long-term survival benefit in a recent phase III trial (Day et al. 2013). The use of adjunctive interferon (IFN)-γ with AmBd and 5FC leads to even faster rates of clearance and can be considered in refractory cases (Perfect et al. 2010; Jarvis et al. 2012). In organ transplant recipients on concomitant nephrotoxic drugs, liposomal AmB (3–4 mg/kg/d) should be substituted for the deoxycholate preparation (Perfect et al. 2010). Where 5FC is not available, fluconazole 800–1200 mg/d can be combined with AmBd (Pappas et al. 2009; Loyse et al. 2012; Day et al. 2013). Where AmBd cannot be safely administered for 14 d, alternatives include shorter (5–7 d) courses (Muzoora et al. 2012) or the oral combination of fluconazole 1200 mg/d plus 5FC (Nussbaum et al. 2010), currently undergoing phase III randomized controlled trials in Africa (see www.controlled-trials.com/ISRCTN45035509).

Following induction treatment, 8-wk consolidation therapy with fluconazole 400 mg/d is recommended, followed by maintenance treatment with 200 mg/d for 6–12 mo or, for HIV-
infected patients, until immune restoration with CD4 count >100 cells/μL with an undetectable viral load on antiretroviral therapy (ART) (Perfect et al. 2010).

Minimize Drug Toxicity

Patients should have regular monitoring of complete blood count, electrolytes, and renal function. Amphotericin B deoxycholate is nephrotoxic, resulting in rising creatinine and potassium and magnesium wasting within days of starting treatment (Gallis et al. 1990). This predictable adverse event can be minimized by using preemptive daily fluid loading with 1 L normal saline (Branch 1988; Mayer et al. 2002) and potassium and magnesium replacement (Girmenia et al. 2005), increasing hydration, and omitting doses if the creatinine rises greater than twofold from baseline (see WHO cryptococcosis guidelines, www.who.int/hiv/pub/cryptococcal_disease2011/en) or switching to liposomal AmB preparations for the remainder of treatment (Perfect et al. 2010). 5FC levels should be monitored, where available, and its dose should be adjusted in renal impairment as drug accumulation increases the risk of bone marrow toxicity (Perfect et al. 2010). AmBd-induced anemia is a significant and less well-recognized adverse effect, resulting in a drop in hemoglobin from baseline of 2–3 g/dL (Joly et al. 1996; Sharkey et al. 1996; Leenders et al. 1998; Bicanic et al. 2008), which may necessitate transfusion. Adverse effects are reversible on stopping treatment (Bicanic et al. 2008). Maintenance dose fluconazole is well tolerated with few drug interactions.

Manage Raised Intracranial Pressure

Raised ICP (defined as CSF opening pressure >20 cm H₂O) is extremely common in CM, occurring in 60%–80% of patients in the context of high fungal burden (Graybill et al. 2000; Bicanic et al. 2009b) causing CSF outflow obstruction and a communicating hydrocephalus, and is associated with mortality (Graybill et al. 2000; de Vedia et al. 2013). Associated morbidities of visual and hearing loss are sometimes profound and irreversible (Rex et al. 1993; Graybill et al. 2000). All patients should have a baseline lumbar puncture with CSF opening pressure (OP) measurement (Fig. 1) (Perfect et al. 2010). Daily therapeutic lumbar punctures, up to a maximum of 20–30 mL CSF, for those with persistently raised OP >25 cm H₂O, provide immediate symptom relief as well as possibly abrogating the adverse impact of raised ICP on survival (Jarvis et al. 2014). Those with refractory high CSF OP and progressive visual or other neurological impairment should be considered for a temporary lumbar drain (Perfect et al. 2010).

Restore Host Immunity while Managing Excessive Inflammation

Patients with cryptococcosis are usually immunocompromised, either iatrogenically in organ transplantation, or through CD4 T-cell loss in HIV infection. Production of proinflammatory cytokines tumor necrosis factor α and interferon-γ via CD4 T-cell macrophage interactions is important for fungal clearance and survival (Jarvis et al. 2013b). Adjunctive IFN-γ augments the clearance of infection by AmBd and 5FC (Jarvis et al. 2012). Restoration of host immunity, either by cautiously lowering doses of

Figure 1. Bedside measurement of CSF opening pressure at lumbar puncture using a manometer.
immunosuppressive agents in solid organ transplant recipients (Snydman et al. 2008) or by commencing ART in HIV-infected patients, is needed to completely clear the cryptococcal infection.

The timing of ART commencement should be individually tailored following induction therapy of CM. Exact timing (between 2–6 wk from start of induction CM treatment, as per the WHO guidelines, www.who.int/hiv/pub/cryptococcal_disease2011/en) depends on the fungal burden at presentation and induction antifungal regimens used, resolution of symptoms and presence of concomitant opportunistic infections, in order to balance the risks of too little versus excessive immune responses in the form of IRIS. A recently completed phase III trial showed excess mortality whether ART is commenced very early at 1–2 wk, median 9 d from start of AmBd-based therapy, compared to 5 wk (Boulware et al. 2013).

An ongoing phase III trial is examining the role of adjunctive steroids in acute CM (see www.controlled-trials.com/ISRCTN59144167). Steroids are currently not recommended to treat acute CM or raised ICP, but are recommended in cases of CM-IRIS refractory to antifungal therapy and management of raised ICP (prednisolone 0.5–1.0 mg/kg/d, tapered over 2–6 wk) (Perfect et al. 2010).

Prevent CM Unmasked by ART Using CRAG Screening and Preemptive Treatment

The simple and inexpensive cryptococcal polysaccharide antigen (CRAG) test has excellent sensitivity and specificity for detection of CRAG in serum, plasma, and CSF (Jarvis et al. 2011b). Cryptococcal antigenemia, indicating early dissemination from the lung, precedes symptomatic meningitis by weeks to months (French et al. 2002), with reported prevalence in cohorts of HIV-infected patients with CD4 < 100 cells/μL ranging between 2% and 21% (Meya et al. 2010; Jarvis et al. 2011a). In many countries in sub-Saharan Africa with high prevalence of HIV and cryptococcal coinfection where patients start ART at very low CD4 counts, an increasing proportion of CM now occurs as unmasking disease following commencement of ART (Jarvis et al. 2010). Reflex CRAG screening of all ART-naïve patients with CD4 < 100 cells/μL with lumbar puncture (LP) to rule out meningitis and preemptive fluconazole therapy at 800 mg/d before ART start is likely to be a cost-effective intervention (Meya et al. 2010; Jarvis et al. 2013a), and is being piloted in centers in South Africa and Uganda.

Address Complications Contributing to Persistent or Relapsed Infection

Patients may either be slow to respond to initial treatment, or relapse following an initial response to therapy, either before or after starting ART. Factors causing slow response to induction therapy of CM include use of drugs that are slow to sterilize the CSF, such as fluconazole-based regimens or poor adherence to consolidation or maintenance therapy, and raised ICP, which can develop on therapy and persist even beyond the point of CSF sterilization (Bicanic et al. 2009b).

For slow clearance despite appropriately dosed AmB-based induction regimens, prolongation of the induction course or adjuvant IFN-γ may be considered (Perfect et al. 2010). Raised ICP usually responds to repeated large volume therapeutic LPs so long as tolerated by the patient, or temporary lumbar drains (Perfect et al. 2010). VP shunting is rarely indicated.

In immunocompetent patients with C. gattii infections, cryptococcomas in lung or brain may respond poorly to antifungal therapy alone, even when administered for the recommended 6 wk. Large cryptococcomas may require steroids and/or debulking surgery for associated mass effect (Perfect et al. 2010).

The development of antifungal drug resistance is rare in the context of AmB-based induction regimens, but has been described following use of fluconazole monotherapy for induction (Bicanic et al. 2006). Minimum inhibitory concentration (MIC) testing of the initial C. neoformans strain is not recommended. For a patient suffering a relapse during fluconazole therapy, paired initial and relapse isolate fluconazole MIC testing is recommended. An MIC
rise > 2 dilutions from baseline, or absolute values > 16 μg/mL suggest development of resistance to fluconazole (Perfect et al. 2010), and patients should be retreated with an AmBd-based induction regimen followed by maintenance on weekly AmBd 1 mg/kg (Powderly et al. 1992). Relapses following ART with negative cultures of CSF should be managed as IRIS following exclusion of alternative diagnoses, with continuation of ART and antifungal therapy, management of raised ICP and consideration of steroids in refractory cases.

REFERENCES


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