Cryptococcal meningitis

Cryptococcal meningitis is caused by one of two closely related environmental fungi, *Cryptococcus neoformans* and *C. gattii*. *C. neoformans* has a world-wide distribution, while *C. gattii* is concentrated in tropical and sub-tropical zones (although *C. gattii* infections have recently emerged on Vancouver Island and the adjacent mainland in British Columbia, Canada). The frequency and circumstances of human exposure to these organisms are not precisely understood, but exposure is assumed to occur following inhalation for the environment from 3-4 years of age and to be nearly universal. Infection is usually controlled effectively by the immune system, but remains latent, so that, if immune function later wanes, due to HIV/AIDS, immunosuppressing medication, or another condition, disease develops, in particular a life-threatening meningitis or meningoencephalitis. *C. neoformans* causes most infections in HIV-infected patients; *C. gattii*, in particular, also causes disease in apparently immunocompetent persons. Person to person transmission does not occur.

**Incidence**
Cryptococcal meningitis remains a very common in patients with late stage HIV-infection. Despite expansion of antiretroviral programmes, cases have not decreased in most African countries. Furthermore, treatment is unsatisfactory: in Africa, mortality has ranged from 24% at 10 weeks to 95% at 12 weeks depending on the initial therapeutic regimen (see table, below). A recent CDC analysis estimated that in Africa, cryptococcosis-associated mortality at 3 months is ~70%\(^1\). The combination of high incidence and difficulties with treatment result in cryptococcosis being a very common cause of death in AIDS patients, accounting for 13 and 17% of all deaths in two cohorts of HIV patients from Uganda. In comparison, TB caused 6% and 5% of deaths respectively, in these studies. While tuberculosis is much more common, treatment is available and effective; the high case fatality rate for cryptococcosis leads to a high death toll. The CDC analysis estimated that HIV-related cryptococcal disease (primarily meningitis) is associated with 600,000 deaths per year globally, over 500,000 in Sub-Saharan Africa alone.
Clinical Features
HIV-associated cryptococcal meningitis usually presents in late stage patients (CD4 cell count <100 cells/μl) as a subacute meningoencephalitis with symptoms progressing over 1-2 weeks. These include headache, fever, and malaise and later, vomiting, double vision, reduced vision, seizures and altered mental status. Signs, if present, may include meningism, papilloedema, cranial nerve palsies (particularly 6th nerve palsies reflective of raised cerebrospinal fluid (CSF) pressure, which is a very common complication) and reduced conscious level.

In non HIV-infected patients, and especially in apparently immune-competent patients with C. gattii infection, the duration of presenting symptoms may be longer, and focal neurological lesions, hydrocephalus, and focal lung lesions are more common, reflective of an increased host inflammatory response, compared with HIV-infected patients.

Lung involvement is probably under-recognised, especially in HIV-infected patients. Immunocompetent patients may present with localized, self-limiting lung nodules, while in the immunocompromised, lung involvement is more diffuse and progressive and often leads to dissemination. In addition to the central nervous system and lung, just about any other organ system can be involved, including skin, lymph nodes and bone.

Diagnosis of cryptococcosis
Diagnosis of cryptococcal meningitis is usually not a problem in HIV-infected patients, if a lumbar puncture is done, since the organism load is high. A simple, quick, and widely available, Indian ink examination of the cerebrospinal fluid (CSF) is positive in around 70-80% of AIDS patients, while those with infection who are India Ink negative are invariably positive on antigen testing and culture of the CSF. However, lumbar puncture is moderately invasive and may require travel to a referral centre, meaning that in many patients presenting with a headache to primary care clinics, diagnosis is initially delayed, with potentially fatal consequences.

However, cryptococcal antigen is also positive in blood in nearly all patients with HIV-associated cryptococcal meningitis and is detectable in urine in most patients. While previously, antigen testing was done using a latex agglutination format requiring some processing of the blood sample in a central laboratory, a new point-of-care, “dipstick” antigen test, is both more sensitive and potentially much more widely accessible. This new test could enable rapid diagnosis even in primary care settings and rapid referral for assessment and earlier treatment.

In non-HIV-associated disease, especially in apparently immune-competent patients, the sensitivity of all diagnostic tests is reduced due to lower organism loads and the diagnosis is occasionally difficult to exclude. Large-volume CSF cultures and repeated lumbar punctures may occasionally be needed in this setting.
Treatment of Cryptococcal Meningitis

Daily intravenous amphotericin B (1mg/Kg/d) plus 6-hourly oral flucytosine (100mg/Kg/d) remain the gold standard for induction therapy, as this combination results in the most rapid control of infection. In HIV-infected patients, after 2 weeks, given the duration-dependent side effects of amphotericin B and flucytosine, patients should be switched to fluconazole. Although less rapidly fungicidal, fluconazole is well tolerated and widely available even in resource-limited settings, through a donation programme. If flucytosine is not available, fluconazole at 800mg/d can be given with amphotericin B as an alternative induction therapy.

Unfortunately in many centres in Africa, 2 weeks induction therapy with amphotericin B cannot be safely sustained. In addition to the costs of the drug, which may be substantial in local terms, there are the requirements for hospitalization and intravenous drug administration. Nursing time and expertise in siting and maintaining IV access for a drug which causes considerable phlebitis, additional IV fluid and electrolyte replacement, and regular, rapid and reliable laboratory monitoring for renal function, electrolytes, and haemoglobin are all significant hurdles for many places. Without proper monitoring, amphotericin B can lead to fatal hypokalaemia. In these circumstances, amphotericin B courses of 5-7 days may have very significant benefit while being much less toxic and requiring less intense monitoring.

In the absence of amphotericin B, high dose oral fluconazole (1200 mg/d for the first 2 weeks) plus flucytosine is more effective than fluconazole alone. However, since flucytosine is not currently widely available, fluconazole monotherapy is still the most widely used initial treatment across Sub-Saharan Africa. 10-week mortality with this treatment, even using the higher doses of fluconazole now recommended, is in the order of 50-60%.

Antiretroviral therapy and maintenance therapy

In HIV-associated meningitis, fluconazole is given at 400-800 mg/d for 2 to 10 weeks, then at 200 mg/d until immune reconstitution has occurred with antiretroviral therapy. Antiretroviral therapy is currently started after 2 to 6 weeks of antifungal treatment, in order to prevent other HIV-related complications without exacerbating immune reconstitution reactions.

Raised intracranial pressure

Raised CSF pressure is extremely common and, if untreated, is associated with worse symptoms and increased acute mortality. There is good evidence that careful mechanical drainage with repeated lumbar punctures (or, in the most severe cases, a lumbar drain or intraventricular drain) relieves symptoms and reduces mortality. However, across Africa, manometers to measure CSF pressure are not generally available, and, although attempts to
measure and manage CSF pressure using intravenous giving sets have been made, currently CSF pressure is not managed in most resource limited settings.

*Alternative amphotericin B formulations*
Lipid formulations of amphotericin B (ie liposomal amphotericin B 3-4mg/kg/d) can be used in place of conventional amphotericin B and are less nephrotoxic, although not more effective. They are preferred for cryptococcal meningitis in patients immunosuppressed through organ transplantation, who do not tolerate conventional amphotericin B well. Amphotericin B-based induction is often prolonged beyond 2 weeks in these cases, and in the non-HIV, non-transplant patient group including those who are immune-competent and those infected with *C. gattii*.

Patients with severe non-meningeal cryptococcosis should also be treated initially with amphotericin B, while for localized or less severe, non-meningeal infection, fluconazole is effective.

*Treatment Outcomes*
Untreated, cryptococcal meningitis is invariably fatal. If diagnosed rapidly, treated initially with amphotericin B plus flucytosine and with CSF pressure managed pro-actively, the 10-week mortality is probably around 20%, as reflected in results from studies from the USA and Europe (see table below). In patients treated late, with fluconazole monotherapy, the outcome is much worse- >50% 10 week mortality, as reported below, in series from Africa. *C. gattii* infections also probably respond less well. In those with underlying disease that cannot be controlled (ie lymphoma or untreated HIV infection), the outcome is also poor.

**Table 1:** Outcomes of therapy for HIV-associated cryptococcal meningitis in developed country settings.

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Year</th>
<th>Induction Treatment</th>
<th>2 week mortality</th>
<th>10 week mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Saag, 1992a</td>
<td>1988-1989</td>
<td>Amphotericin B 0.4-0.5mg/kg/d +/- Flucytosine 150mg/kg/d, or fluconazole 200-400 mg/d</td>
<td>12%</td>
<td>17%</td>
<td>*lethargy or obtundation Comatose patients and those unlikely to survive 2 weeks excluded.</td>
</tr>
<tr>
<td>USA</td>
<td>Van der Horst, 1997b</td>
<td>1991-1994</td>
<td>Amphotericin B 0.7mg/kg/d +/- Flucytosine 100mg/kg</td>
<td>5.5%</td>
<td>10-23%*</td>
<td>Comatose patients excluded. *exact 10 week mortality unknown as only subset of patients re-randomized at 2 weeks</td>
</tr>
<tr>
<td>USA</td>
<td>Robinson, 1999c</td>
<td>1986-1993</td>
<td>Amphotericin B 0.3-0.7mg/kg/d + Flucytosine 150mg/kg/day</td>
<td>12%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>Lortholary 2006d</td>
<td>1990-1996</td>
<td>Amphotericin based therapy 75%, fluconazole monotherapy 25%</td>
<td>---</td>
<td>19%</td>
<td>No difference between pre-ART and ART era (21% vs 18%).</td>
</tr>
<tr>
<td>France</td>
<td>Dromer, 2008e</td>
<td>1997-2001</td>
<td>Amphotericin B + 5FC 52%, Amphotericin B monotherapy or fluconazole monotherapy in the remainder</td>
<td>6.5%*</td>
<td>15%**</td>
<td>*Just HIV positive patients. **12 week data.</td>
</tr>
</tbody>
</table>
Table 2: Outcomes of therapy for HIV-associated cryptococcal meningitis in resource-limited settings

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Year</th>
<th>Induction Treatment</th>
<th>2 week mortality</th>
<th>10 week mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>Imwidthaya, 2000</td>
<td>1996-1997</td>
<td>Amphotericin B 0.5-0.8mg/kg/d</td>
<td>-----</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Pitisutthum, 2001</td>
<td>1997-1999</td>
<td>Amphotericin B 0.7mg/kg/d</td>
<td>16%</td>
<td>~40%*</td>
<td>*Exact 10 week figure not reported.</td>
</tr>
<tr>
<td>Thailand</td>
<td>Brouwer, 2004</td>
<td>2002</td>
<td>Amphotericin B +/- Flucytosine 100mg/kg/d and/or fluconazole 400mg/d</td>
<td>14%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Cambodia</td>
<td>Micol, 2007</td>
<td>2004</td>
<td>Amphotericin B 0.7mg/kg/d</td>
<td>10%*</td>
<td>37%**</td>
<td>*3 and **12 week figures.</td>
</tr>
<tr>
<td>Peru</td>
<td>Dammert, 2008</td>
<td>1998-2001</td>
<td>Amphotericin B 0.7mg/kg/d</td>
<td>13%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Zambia</td>
<td>Mwaba, 2001</td>
<td>1998-1999</td>
<td>Fluconazole 200mg/d*</td>
<td>39%</td>
<td>96%**</td>
<td>*Data only reported for those who received treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluconazole 200mg/d</td>
<td></td>
<td></td>
<td>**400mg stat dose initially. **12 week figure</td>
</tr>
<tr>
<td>Uganda</td>
<td>Mayanja-Kizza, 1998</td>
<td>1994</td>
<td>Fluconazole 200mg/d</td>
<td>40%</td>
<td>64%*</td>
<td>*8 week figure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluconazole 200mg/d + 5FC</td>
<td>16%</td>
<td>44%*</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>Schaars, 2006</td>
<td>1999-2002</td>
<td>Fluconazole 200mg or 400mg/d</td>
<td>25%**</td>
<td>~50%***</td>
<td>**In hospital. *** median follow up for discharged patients 36 days, lost=censored</td>
</tr>
<tr>
<td>South Africa</td>
<td>Bicanic, 2007</td>
<td>2005</td>
<td>Amphotericin B 1mg/kg/d*</td>
<td>17%</td>
<td>37%</td>
<td>*Amphotericin only given for 1 week. 5 of 54 patients received fluconazole as initial therapy.</td>
</tr>
<tr>
<td>Uganda</td>
<td>Kambugu, 2008</td>
<td>2001-2002</td>
<td>Amphotericin B 0.7mg/kg/d</td>
<td>46%</td>
<td>-----</td>
<td>Comatose patients excluded.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2006-2007</td>
<td></td>
<td>20%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>Bicanic, 2008</td>
<td>2005-2006</td>
<td>Amphotericin B 0.7-1mg/kg/d plus Flucytosine 100mg/kg/d</td>
<td>6%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Botswana</td>
<td>Bisson, 2008</td>
<td>2005-2006</td>
<td>Amphotericin B 1mg/kg/d</td>
<td>17%*</td>
<td>-----</td>
<td>*In hospital figure</td>
</tr>
<tr>
<td>Uganda</td>
<td>Longley, 2008</td>
<td>2005-2007</td>
<td>Fluconazole 800mg/d</td>
<td>37%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluconazole 1200mg/d</td>
<td></td>
<td>22%</td>
<td>48%</td>
</tr>
<tr>
<td>Malawi</td>
<td>Jackson, 2012</td>
<td>2008</td>
<td>Fluconazole 1200mg/d</td>
<td>37%</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fluconazole 1200mg/d + 5FC 100mg/kg/d</td>
<td>10%</td>
<td>43%</td>
<td></td>
</tr>
</tbody>
</table>
Opportunities to reduce Global Disease Burden and improve patient outcomes:

A number of feasible initiatives, if widely implemented, could have a very substantial impact on reducing the global cryptococcal disease burden:

1. Prevention of clinical disease in those newly diagnosed with HIV with a low CD4 cell count (<100) through screening for cryptococcal antigen prior to initiation of antiretroviral therapy; and pre-emptive fluconazole therapy in those patients who test antigen positive (around 5% in many settings). Recent research has shown:
   a. Over 50% cases in S Africa currently present AFTER a diagnosis of HIV has been made.
   b. Antigen screening after an HIV diagnosis, before antiretroviral therapy, identifies those at risk of developing meningitis – 0/660 Ag negative patients developed meningitis, compared with 7/25 antigen positive patients.
   c. The strategy is highly cost-effective. The strategy has been endorsed for high incidence areas in WHO guidance (reference above), and is being implemented in South Africa.

2. Earlier diagnosis of all symptomatic cases through widespread use of new point-of-care antigen test in primary care as well as secondary care settings.

3. Optimization of antifungal therapy in resource limited settings through:
   a. Training and operational research on safe delivery of amphotericin B-based therapy (detailed advise on pre-emptive management of known toxicities is given in WHO guidelines).
   b. Increased access to flucytosine. Abandonment of fluconazole monotherapy and replacement with amphotericin B-based therapy (for one or two weeks depending on resource), or oral combination therapy with fluconazole and flucytosine, would likely substantially reduce the 10 week mortality from around 60% seen with fluconazole alone towards the 30-35% seen with amphotericin B-based combination treatment.

4. Systematic measurement and management of cerebrospinal fluid pressure through increased access to manometers in resource limited settings of high burden.

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