Cryptococcal meningitis

Cryptococcal meningitis is a common opportunistic infection with a worldwide distribution. Patients with human immunodeficiency virus (HIV) infection are among those at highest risk of developing clinical disease. Outcomes vary significantly but the 90-day mortality can reach 21% in high-resource settings and 70% in resource-limited settings in sub-Saharan Africa (Brizendine et al, 2013; Park et al, 2009). This article discusses the essentials in the diagnosis and management of this infection.

Epidemiology and clinical features

The environmental fungi *Cryptococcus neoformans* and *C. gattii* are the cause of cryptococcosis. These organisms have a ubiquitous distribution and are found particularly concentrated in soil associated with bird excreta and within certain trees.

The inhalation of spores or yeast cells by individuals is frequently asymptomatic and in most cases subsequent infection is localized and contained with the lungs. However, in susceptible hosts reactivation or progressive infection can occur, leading to disseminated disease. Patients with HIV infection and a CD4 cell count fewer than 100 cells/μl are at highest risk of cryptococcosis (Jarvis and Harrison, 2007). This population accounts for the majority of the global burden of disease. Other immunosuppressive states, namely chronic steroid use, solid organ transplant recipients and organ failure, are risk factors but to a lesser degree (Bratton et al, 2012). Cryptococcal meningitis in HIV-negative patients without classical risk factors, especially with *C. gattii*, is increasingly recognized (Harris et al, 2013). The mechanisms of infection in this predominantly male cohort are poorly understood but may relate to incompletely-defined deficiencies in cellular-mediated immunity (Panackal et al, 2015).

The global distribution of cryptococcal disease mirrors the HIV pandemic, with the majority of cases occurring in sub-Saharan Africa. Despite improved access to antiretroviral therapy an estimated 100 000–200 000 deaths per year can be attributed to cryptococcosis. Estimates suggest that up to 280 cases of cryptococcal meningitis occur within the UK each year (Antinori et al, 2014).

Although cryptococcosis affects all body sites the most common presentation is a meningoencephalitis, which is more acute in patients with HIV infection. This manifests as an insidious headache usually spanning several weeks, along with neck stiffness, somnolence and altered cognitive function. Fever may be absent from the initial presentation, especially in HIV-negative patients. Features related to increased intracranial pressure such as abducens nerve palsy occur, along with visual and hearing impairment.

Diagnosis

Early diagnosis reduces mortality. Suspicion of cryptococcal meningitis in patients at risk should prompt urgent lumbar puncture and CSF analysis.

If at all possible, computed tomography and/or magnetic resonance imaging brain scans should be done before lumbar puncture in immunocompromised patients. This will exclude space-occupying cryptococcomas or obstructive hydrocephalus, both much more common in HIV-uninfected patients with cryptococcal meningitis. In HIV-infected patients, raised CSF pressure is not associated with increased ventricular size and radiological changes are often non-specific (Loyse et al, 2015).

The opening pressure is raised (>20 cmH_2O) in the majority of cases of cryptococcal meningitis and CSF cellular analysis may show a modest (<50 white cells/μl) increase in mononuclear cells. In patients with HIV infection the white cell count may be normal reflecting a paucity of inflammation. The protein level is usually raised and the glucose level is low or normal.

India ink examination of the CSF is positive in up to 70% of cases although this value is dependent on both the operator and fungal burden, which tends to be higher in patients with HIV infection. Testing for cryptococcal antigen polysaccharide in CSF has increased the sensitivity and specificity of diagnosis to 98%, and may be more sensitive than culture in certain situations (Perfect and Bicanic, 2015). Cryptococcal antigen polysaccharide testing has been greatly facilitated by the development of a point-of-care, lateral flow 'dipstick' format (Jarvis et al, 2011). Although a high cryptococcal antigen polysaccharide titre (>1:1024) is suggestive of heavy infective burden and poor prognosis, serial measurements are unhelpful for management and can remain positive after elimination of viable organisms (Powderly et al, 1994). Serum testing for cryptococcal antigen polysaccharide could be helpful in otherwise asymptomatic but high-risk patients, and if positive should prompt further investigations including lumbar puncture.

Cryptococcus grows readily on standard Sabouraud agar inoculated with CSF or blood at room temperature, and this is important in confirmation of diagnosis. However, growth may take several days and treatment should not be delayed, especially with the widespread availability of cryptococcal antigen polysaccharide testing. Evidence of a negative CSF culture is important in the management of late disease complications when it may be difficult to differentiate between recurrence and immune reconstitution.

Cryptococcal meningitis can be the first presentation of HIV infection or other

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Table 1. Treatment for cryptococcal meningitis

Phase	Drug	Usual dose
Induction (2 weeks*)	Amphotericin B deoxycholate†	1 mg/kg/day
	with flucytosine‡	100mg/kg/day in four divided doses orally
Consolidation (8 weeks)	Fluconazole	400 mg/day orally
Maintenance	Fluconazole	200 mg/day orally

** >2 weeks for transplant-associated cryptococcal meningitis, 4–6 weeks for non-HIV non-transplant cryptococcal meningitis (Perfect et al, 2010). †Liposomal amphotericin B at 4 mg/kg/day can be substituted. ‡Fluconazole 800–1200 mg/day orally may be an acceptable substitute where flucytosine is not available.*

underlying immune deficiency. In situations where a patient with HIV established on antiretroviral therapy presents with an opportunistic infection, a detailed history into medication concordance as well as investigations into virological failure and drug resistance should be undertaken.

Management

Careful attention to the basics of patient care is important across all settings. Interventions including patient positioning to avoid aspiration, care of pressure areas and feeding via a nasogastric tube are important in patients who present with a decreased level of consciousness. Judicious management of fluid and electrolyte balance in the context of treatment nephrotoxicity, relief of symptoms resulting from raised intracranial pressure through therapeutic lumbar puncture (provided there are no contraindications), analgesia and the control of seizures are also essential aspects of care.

The initial treatment of HIV-associated cryptococcal meningitis involves a 14-day induction phase with combination amphotericin B with flucytosine, as shown in *Table 1* (Day et al, 2013). For non-HIV-infected patients, the recommended duration of induction is longer, up to 4–6 weeks (Perfect et al, 2010).

The liposomal formulations of amphotericin, e.g. AmBisome, are less prone to inducing acute kidney injury and electrolyte loss when compared to amphotericin B deoxycholate. This may be significant in the context of longer induction treatment and in patients who are taking concurrent nephrotoxic immunosuppressive agents, e.g. ciclosporin and tacrolimus, which are often continued in the induction treatment phase.

In populations where risk factors for renal injury are lower, evidence suggests amphotericin B deoxycholate is equally efficacious (Hamill et al, 2010). Administration of 1 litre of 0.9% normal saline per day in addition to usual fluid requirements, along with routine potassium (60 mEq/d) and magnesium (16 mEq/d) supplementation, reduces adverse renal effects (World Health Organization, 2011). However, anaemia associated with amphotericin B deoxycholate remains a concern, especially where capacity for blood transfusion is limited (Bicanic et al, 2015). Notably amphotericin B deoxycholate is several times less expensive than the liposomal versions (amphotericin B deoxycholate costs £10/day *vs* AmBisome at £696/day), which has a significant impact on access to medicines, especially in low-resource settings.

Flucytosine use is well tolerated at 100 mg/kg/day for 2 weeks, and is associated with a significant reduction in mortality (Day et al, 2013). However, it can also be associated with bone marrow suppression and dose reduction may be required in the context of significant renal impairment. In many countries flucytosine may not be available and fluconazole at 800–1200 mg orally per day may be an alternative adjunct to amphotericin (Pappas et al, 2009) although its efficacy is still under evaluation.

Raised intracranial pressure during treatment is associated with poor outcomes and manifests with increased headache, obtundation and vomiting. Management of intracranial pressure through therapeutic drainage of CSF improves patient outcomes (Jarvis et al, 2014) and importantly will help relieve otherwise intractable headaches.

When the initial lumbar puncture opening pressure is greater than 30 cmH_2O then CSF can be safely removed at 10 ml increments up to a maximum total of 30 ml at any one time. It is important that the closing pressure is measured between each increment to avoid excessive removal. Therapeutic lumbar punctures may have to be repeated daily and occasionally if opening pressure remains persistently raised a temporary lumbar drain may need to be considered. Dexamethasone and acetazolamide as adjunctive treatments for raised intracranial pressure in cryptococcal meningitis have not shown any benefit in clinical trials (Newton et al, 2002; Beardsley et al, 2016). Some authorities recommend that a lumbar puncture should be repeated on or before day 14 to ensure CSF sterilization. Furthermore raised CSF pressure may develop in the second week despite adequate treatment.

Fluconazole 400 mg a day orally is given for the consolidation phase for a further 8 weeks, which is reduced to 200 mg thereafter as secondary prophylaxis. The optimal duration of fluconazole is unclear but some advocate stopping after a minimum of 1 year if there is sufficient immune constitution (CD4 >200 cells/μl) for more than 6 months in patients with HIV infection, or if the underlying immunosuppression is removed in HIV-negative patients.

Sertraline, an antidepressant, has been shown to improve cryptococcal clearance from the CSF when used as an adjunct in the treatment of cryptococcal meningitis (Rhein et al, 2016). However, further studies are required to investigate if this translates into improved clinical outcomes.

Late complications

Patients with HIV infection and low CD4 cell counts need to start antiretroviral therapy early to prevent further complications arising from other opportunistic infections, but this has to be balanced with the risk of immune reconstitution inflammatory syndrome (cryptococcal meningitis-immune reconstitution inflammatory syndrome) which can present with worsening headaches, fevers and photophobia. Evidence suggests the optimum timing of starting antiretroviral therapy is between 4–6 weeks from the start of cryptococcal meningitis treatment (Boulware et al, 2014).

Clinically it is often difficult to differentiate between cryptococcal meningitis-immune reconstitution inflammatory syndrome and disease recurrence given the similar presentations and features of raised intracranial

pressure. Testing of CSF cryptococcal antigen polysaccharide is unhelpful as it may remain positive as a result of fungal antigen persistence. Patients are therefore usually restarted on the induction regimen again with continuation of antiretroviral therapy until CSF sterility is demonstrated through negative culture. Careful exclusion of other opportunistic infections and their corresponding unmasking immune reconstitution inflammatory syndrome reactions (tuberculosis and cerebral toxoplasmosis) is required.

Ongoing management for cryptococcal meningitis-immune reconstitution inflammatory syndrome may involve therapeutic lumbar punctures and, in selected cases, short courses of corticosteroids. Similar processes can also occur in HIV-negative patients recovering from cryptococcal meningitis who have their immunosuppressive medications reduced, and in apparently immunocompetent patients following initial clinical improvement (Panackal et al, 2015).

Conclusions

Cryptococcal meningitis is associated with a significant worldwide mortality as well as vision and hearing loss in survivors. For clinicians who practice in low resource settings, the limited availability of antifungal drugs and the requirement for close monitoring and management of adverse effects are key challenges. Further advocacy and studies are required (Loyse et al, 2013). Although cryptococcal meningitis is relatively uncommon in the UK this makes it all the more important for the clinician to rapidly recognize and treat this devastating disease effectively. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Cryptococcal meningitis is an important differential diagnosis in immunocompromised patients who present with a headache or fever and in any patient with a lymphocytic meningitis.
- A lumbar puncture, India ink staining, culture, and CSF and blood testing for cryptococcal antigen polysaccharide are useful tests. A new lateral flow cryptococcal antigen polysaccharide test is more rapid and sensitive than older latex agglutination tests.
- The gold standard treatment is amphotericin B combined with flucytosine for 2 or more weeks, followed by 8 weeks of consolidation, and then maintenance treatment with fluconazole.
- Management of raised intracranial pressure with careful therapeutic lumbar punctures will improve patient symptoms and outcome.
- Immune reconstitution reactions can arise in both HIV-infected and non HIV-infected patients several months on. Such reactions need to be differentiated from ongoing active infection, and in select cases may require and respond to corticosteroids.