REVIEW

Cryptococcal meningitis

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INTRODUCTION

The HIV pandemic has raised the profile of *Cryptococcus neoformans* from an obscure yeast to the most important fungal cause of morbidity and death worldwide. Previously described as a rare cause of meningitis in the tropics, or in patients with some form of acquired immunodeficiency such as haematological malignancy or organ transplantation, cryptococcal meningitis is now a significant public health burden in developing countries. 20% of all AIDS deaths are due to cryptococcal meningitis, making it

the second most common cause of death in HIV infection after tuberculosis (French *et al.* 2002). Moreover, despite the availability of highly active antiretroviral therapy (HAART), it continues to pose difficult management questions in the industrialized world. Questions remain for physicians regarding the optimal combination of antifungal agents, duration of treatment, accurate indicators of response to therapy, management of raised intracranial pressure, and the role of adjunctive therapies such as corticosteroids or other anti-inflammatory agents.

MICROBIOLOGY

The genus *Cryptococcus* contains at least 39 species of yeast, but few are able to cause disease in humans (Casadevall & Perfect 1998). Even those that do cause infection are not primarily pathogens, they have so-called 'ready-made virulence' as a side-effect of their adaptation to their environments. Most human infections are due to *C. neoformans*. Disease has very rarely been attributed to other species such as *C. flavescens* (formerly *laurentii*). *C. neoformans* is an encapsulated yeast first identified as a human pathogen in 1894 when it was isolated from the tibia of a patient in Germany by Busse and Buschke (Mitchell & Perfect 1995). The same year it was also isolated from peach juice by Sanfelice (Mitchell & Perfect 1995). The first description of cryptococcal meningitis was published in 1905 by von Hansemann, although a case of chronic meningitis described in 1861 by Zenker, prior to the pathogen isolation, was probably the first case history (Mitchell & Perfect 1995; Casadevall & Perfect 1998).

Cryptococcus neoformans is dimorphic, existing in the asexual yeast form characterized by oval to spherical cells with a polysaccharide capsule, and in the sexual or perfect state characterized by the presence of basidiospores. The sexual form has not been described in association with clinical specimens and is observed only during mating, and mating has only been observed under laboratory conditions. The asexual form reproduces through budding, which is frequently seen in clinical specimens. Some strains produce pseudohyphal forms that may be seen in tissue sections.

C. neoformans is readily cultured in the laboratory, producing mucoid colonies within 36–72 h, although growth is inhibited at 37 °C. Colonies are white to cream in colour, but characteristic dark brown colonies are formed when grown on birdseed agar. The organism grows readily in automated blood culture systems.

There are three varietal forms of *C. neoformans*—*C. neoformans* var *grubii*, *C. neoformans* var *gattii*, and *C. neoformans* var *neoformans*. They are distinguishable by serotyping using rabbit antisera, and by DNA fingerprinting techniques such as amplified fragment length polymorphism analysis (Boekhout *et al.* 1997; Boekhout *et al.* 2001). The different varietal forms are now thought to represent different species (Franzot *et al.* 1999). They have different environmental niches, geographical distributions, and affect different patient groups (Table 1). The vast majority of infections world-wide occur in HIV patients and are due to serotype A (*C. neoformans* var *grubii*). In the absence of serotyping, *var gattii* can be distinguished from *var neoformans* and *var grubii* through growth on canavanine glycine-bromothymol blue agar.

C. neoformans var *grubii* and *C. neoformans* var *neoformans*

Both these varieties predominantly affect the immunosuppressed, and *var grubii* (serotype A) is responsible for the vast majority of infections in HIV-positive patients. Their ecological niche is not well defined, but *C. neoformans* is not primarily a pathogen. It is associated with pigeon droppings and soil. Birds are not thought to develop disease because of their relatively high

Table 1 Varietal forms of *Cryptococcus neoformans*

PATHOGEN	SEROTYPE	GEOGRAPHIC DISTRIBUTION	ENVIRONMENTAL ASSOCIATION	AFFECTED PATIENT GROUPS
<i>C. neoformans</i> var <i>grubii</i>	A	Worldwide	Birds, particularly pigeon excreta	HIV patients (98% of all isolates) Immunosuppressed patients Rarely immunocompetent
<i>C. neoformans</i> var <i>gattii</i>	B, C	Tropics and subtropics	Flowering eucalyptus trees	Immunocompetent patients
<i>C. neoformans</i> var <i>neoformans</i>	D	Worldwide	Birds, particularly pigeon excreta	Immunosuppressed patients Rarely immunocompetent
<i>C. neoformans</i> var <i>grubii</i> /var <i>neoformans</i> hybrid	AD	Not known	Not known	Rare clinical isolate Immunosuppressed

body temperature, which inhibits the growth of *Cryptococcus*.

C. neoformans var gattii

This variety occurs in the tropics and sub-tropics and is found in association with flowering eucalyptus trees such as the red river gum (*Eucalyptus camaldulensis*) (Ellis & Pfeiffer 1990). Disease predominantly occurs in immunocompetent patients and there is a strong male preponderance (Chen *et al.* 2000). Interestingly, there has recently been an outbreak of this infection on Vancouver Island, British Columbia, where the climate is far from subtropical. Mammals other than humans are susceptible to infection with this organism and, perhaps unsurprisingly, infection in koala bears is well documented. However, disease has also been recorded in dolphins in the Vancouver Island outbreak.

SPECTRUM OF DISEASE

While meningitis is by far the most common manifestation of cryptococcal infection, other infectious syndromes are well recognized. They will be described briefly below, but the focus of this article will be on meningitis. Infection is believed to occur through inhalation and the primary site of infection is the lung. It is likely that most such infection is asymptomatic. Primary infection may result in either immediate pulmonary or disseminated disease, or it may be quiescent for many years, with subsequent disease development following an immunosuppressive event later in life. Many of the early case reports were of patients with cancer. Disease has been described in almost all body systems (Table 2) – the first case report was of osteomyelitis, but the brain remains the organ with a particular vulnerability to infection for reasons that are not well understood.

Central nervous system

Meningitis is the most common manifestation of cryptococcal infection. It would be more accurate to describe the syndrome as a meningoencephalitis, since histopathological examination demonstrates that along with the subarachnoid space the brain parenchyma itself is usually involved (Lee *et al.* 1996). Presentation varies, and the diagnosis should be considered in all cases of subacute meningitis (presentation over 2–4 weeks). However, the organism can also cause an acute meningitis occurring over a few days to a week, and a true chronic meningitis, the long-

Table 2 Recognized syndromes caused by *C. neoformans* infection

CENTRAL NERVOUS SYSTEM
Meningoencephalitis – acute/subacute/chronic
Brain abscess (cryptococcomas)
Isolated cranial nerve lesions
Subdural effusion
Spinal cord lesions
Dementia
Ischaemic stroke
RESPIRATORY SYSTEM
Pneumonia
Cavitation
Endobronchial masses
Empyema
Nodules – solitary and multiple
Sinusitis
Mediastinitis
Bronchiolitis obliterans
Pneumothorax
Acute respiratory distress syndrome
SKIN
Papules
Ulcerated lesions
Erythema nodosum
Abscess
RETICULO-ENDOTHELIAL SYSTEM
Lymphadenitis
GASTROINTESTINAL SYSTEM
Pancreatitis
Hepatitis
Peritonitis
Oesophagitis
MUSCULOSKELETAL SYSTEM
Osteomyelitis
Septic arthritis
Myositis
EYE
Endophthalmitis
Papilloedema
Optic nerve atrophy
GENITOURINARY SYSTEM
Pyelonephritis
Prostatitis
CARDIOVASCULAR SYSTEM
Endocarditis
Fungaemia
Myocarditis
Pericarditis
ENDOCRINE SYSTEM
Cushing’s syndrome
Adrenal insufficiency
Adrenal mass lesions
Thyroiditis

est duration of illness recorded being 29 years (Casadevall & Perfect 1998). Other neurological presentations include focal signs secondary to cryptococcoma development, as well as subdural effusions and spinal cord lesions secondary to granuloma. It is important to remember that as well as causing meningitis, cryptococcal infection is one of the causes of reversible subacute dementia (perhaps because of the hydrocephalus although yeasts are found in brain parenchyma), and the diagnosis should be excluded in those patients with a relevant exposure history, such as travel to the tropics, or risk of immunosuppression. Endophthalmitis can occur alone or as part of meningitis. Blindness is a common sequela of infection, particularly in Viet Nam in apparently immunocompetent patients.

Lung

The lung is the second most common organ to develop clinical disease, usually pneumonia, which can occur in the immunocompetent, particularly with *var gattii* infection. Other pulmonary manifestations include solitary nodules, superior vena cava obstruction, cavitation and pleural effusions/empyema – the radiographic appearances can be very similar to pulmonary tuberculosis. HIV patients who are infected with *C. neoformans* tend to present with meningitis rather than pulmonary disease. Although up to one-third of them have an abnormal chest X-ray, pulmonary symptoms are rare (Casadevall & Perfect 1998). *Var gattii* much more commonly causes pulmonary disease (without meningitis) in immunocompetent patients, resembling pulmonary TB. It is extremely unusual for HIV patients to get symptomatic pulmonary disease due to cryptococcal infection.

Skin

The skin is the third most common organ to be affected by cryptococcal infection. Infected skin lesions can have a wide variety of appearances, from papules through to plaques, subcutaneous swellings, sinuses and blisters (Fig. 1). Skin involvement appears to be becoming more common with HIV infection and the lesions often resemble molluscum contagiosum. In fact, other skin diseases may coexist within the same lesion (for example Kaposi's sarcoma). While skin infection can occur following inoculation, for example through needle stick injury, it is generally the result of disseminated cryptococcal infection and so other sites of potential infection such as brain, heart and lungs should be investigated.

Figure 1 Typical skin lesion in a patient with disseminated cryptococcosis.

EPIDEMIOLOGY OF CRYPTOCOCCAL MENINGITIS

Cryptococcosis is a rare infection in healthy human populations. Therefore the prevalence of cryptococcal disease in a population can be considered as an indicator of the degree of immune suppression in that group. Indeed, cryptococcal meningitis is a sentinel for the spread of the HIV pandemic. In common with many hospitals in Asian countries, the Hospital for Tropical Diseases in Ho Chi Minh City has seen a large rise in the number of clinical isolates of *C. neoformans* over recent years that represents the spread of HIV within our community (Fig. 2).

Figure 2 Increasing number of isolates of *C. neoformans* from cerebrospinal fluid compared with *Streptococcus suis*, Hospital for Tropical Diseases, Ho Chi Minh City, 1992–2002.

The HIV pandemic has led to a massive increase in the number of cases of cryptococcal meningitis. Generally, there appears to be a preponderance of males affected, even after adjusting for sex differences in HIV infection, and most cases occur in the 20–50 years old age group (Lewis & Rabinovich 1972). Cryptococcosis is rare in children. Conditions other than HIV that predispose to infection include:

- immunosuppressive therapy associated with organ transplantation;
- sarcoidosis;
- lymphoproliferative disorder;
- hypogammaglobulinaemia;
- corticosteroid therapy;
- systemic lupus erythematosus;
- cirrhosis;
- peritoneal dialysis (Casadevall & Perfect 1998).

The effect of diabetes mellitus on predisposition to cryptococcal meningitis is unclear. Apparently normal patients who develop invasive cryptococcal disease due to serotypes A or D may have some underlying unidentified subtle immune defect (Schimpff & Bennett 1975). However, invasive cryptococcosis due to serotypes A or D probably does occur in otherwise normal individuals, and the incidence is estimated at 0.2 per million people per year (Friedman 1983).

Definitive diagnosis of
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THE HIV PANDEMIC

The HIV pandemic has such a profound impact on the prevalence of cryptococcal disease that it is important to understand its scale. Currently there are 40 million people living with HIV/AIDS (UNAIDS/WHO 2003). The vast majority (27 million) of these are in sub-Saharan Africa where the overall seroprevalence is 7.5–8.5% of 15–49 years olds but this rises to 45% in some

countries. There are 6 million people living with HIV in south and south-east Asia. In 2003 there were 3 million HIV deaths and 5 million new infections worldwide. The epidemic continues to grow rapidly, particularly in south and south-east Asia (up to 1.1 million new infections in 2003) and Russia. Recently it was estimated that in Botswana, where HIV seroprevalence approaches 45%, 9 out of 10 of the current 15-year-old boys will die from HIV infection. In Ho Chi Minh City, Viet Nam, more than 80% of intravenous drug users were HIV positive by the end of 2001.

HIV infection leads to a progressive inexorable fall in CD4 count. A CD4 count of less than 100 cells/ μ L (normal range 500–1500 cells/ μ L) dramatically increases the risk of cryptococcal meningitis. In much of the developing world lack of access to HIV testing and health education means that many patients have CD4 counts substantially lower than this when they present to health services, and so they are already severely immunosuppressed. It should be remembered that absolute CD4 counts should only be taken as a guide to help generate differential diagnoses – individual patients can lose disease-specific immune responses yet have relatively well-preserved CD4 counts, and therefore be at risk of opportunistic infections. While Highly Active Anti-Retroviral Therapy (HAART) is effective in producing meaningful immune reconstitution, it is unavailable to the vast majority of people infected with HIV due to cost and lack of political will. Thus there will be a large rise in the incidence of tuberculosis and opportunistic infections as the pandemic progresses. For example, in parts of Africa up to 90% of adult in-patients on general medical wards are HIV positive, and in Zimbabwe 45% of all meningitis is caused by *Cryptococcus neoformans* (Mwaba *et al.* 2001).

CLINICAL PRESENTATION OF CRYPTOCOCCAL MENINGITIS

The presentation varies. The most frequent symptom in both the immunosuppressed and immunocompetent is headache, occurring in more than 75% of patients. Fever is also common, occurring in more than half of all cases. The duration of symptoms before presentation is likely to be longer in non-AIDS patients, with a history of more than 2 weeks in only 25% of HIV positive patients. Other common symptoms include nausea and vomiting, lethargy, personality change, memory loss, stupor and

coma (Casadevall & Perfect 1998). Neck rigidity seems to be uncommon in HIV patients, occurring in approximately 25%, and focal neurological signs appear in 20% (Friedmann *et al.* 1995). Some African series have reported a higher prevalence of neck stiffness (Moosa & Coovadia 1997). Skin lesions are reported in between 3 and 10% of HIV infected patients. In general, focal neurological signs, neurological sequelae and lung involvement are more common in *var gattii* infections than in *var grubii* or *var neofor-mans* infections (Casadevall & Perfect 1998).

CSF EXAMINATION

Definitive diagnosis of cryptococcal meningitis requires lumbar puncture with demonstration of yeasts with India ink stain, positive cryptococcal antigen testing or culture of the organism. CSF examination generally reveals a mild mononuclear leucocytosis (50–500 cells/ μ L). The CSF protein is rarely greater than 500–1000 mg/dL and it may be normal, especially in HIV patients. In HIV patients, the cell count is usually much lower, and often in single figures. CSF glucose/blood glucose is usually slightly low. One study from Africa found that 17% of AIDS patients with cryptococcal meningitis had normal CSF parameters (Moosa & Coovadia 1997). Clues to HIV infection on routine blood testing include mild anaemia, lymphopenia, thrombocytopenia and raised total protein.

IMAGING

CT brain scan is normal in 50% of patients with cryptococcal meningitis. There are no pathognomonic findings, and the changes may closely resemble those seen in tuberculous meningitis. The most common abnormal finding is hydro-

cephalus. Magnetic resonance imaging is more likely to demonstrate abnormalities than CT scanning (Fig. 3). The appearances may differ depending on the cause of any underlying immunosuppression. For example, in AIDS patients there may be diffuse cortical atrophy, and hydrocephalus is reportedly less common. Cortical atrophy in HIV patients may be a direct consequence of the retroviral infection. Conversely, gyral enhancement is often seen in HIV negative patients. Occasionally focal abnormalities representing cryptococcomas will be seen. Brain imaging is justified to exclude mass lesions and, in the HIV population, other pathology such as toxoplasmosis or CNS lymphoma. The role of serial scans in monitoring response to treatment is unclear (Casadevall & Perfect 1998).

DIAGNOSTIC TECHNIQUES

India ink test

The CSF India ink test is a simple and relatively sensitive test that enables the rapid diagnosis of cryptococcal meningitis. Its low cost makes it suitable for resource-poor settings. A drop of CSF is placed on a slide and mixed with a drop of India ink. A cover slip is placed on the slide, which is examined under an oil immersion lens. Yeast cells are easily identified through the halo effect that occurs around them because of the glucuronoxylomannan capsule (Fig. 4). The sensitivity of the test rises to 75% with centrifugation of the clinical sample. However, a concentration of yeasts less than 10^4 colony forming units (CFU) is unlikely to be detected, and therefore all patients should have CSF fungal culture and cryptococcal antigen testing if resources allow. It is important to note

Figure 3 MRI scan of the brain of an apparently immunocompetent patient with cryptococcal meningitis (a) compared with MRI scan of a patient with tuberculous meningitis (b) showing prominent dilated ventricles with peri-ventricular high signal.

Figure 4 India ink stain of CSF demonstrating many yeast cells of *C. neoformans*, with prominent capsules.

that tuberculous meningitis may occur at the same time as cryptococcal meningitis in AIDS patients, and therefore all patients should have a CSF smear examined for acid and alcohol fast bacilli to exclude TB.

Culture

C. neoformans from CSF or blood grows readily on blood or Sabouraud's agar at 35 °C. Identification can be confirmed through the demonstration of capsule growth on corn meal agar, development of characteristic brown mucoid colonies on birdseed agar, and through commercially available sugar assimilation test kits. Biotyping, to distinguish *var gattii* from *var neoformans* and *var grubii*, can be done relatively cheaply using canavanine-glycine-bromothymol blue agar, although currently this has little clinical relevance (Fig. 5). *C. neoformans* grows easily in commercially available automated blood culture systems. Culture of CSF is more sensitive in detecting cryptococcal infection than the India ink test, with a sensitivity approaching 90%. Positive culture is more likely with larger volumes of CSF.

Cryptococcal antigen

Cryptococcal antigen testing is both sensitive

and specific in identifying patients with cryptococcal disease. Several commercial kits are available, relying on either latex agglutination or ELISA methodologies. The kits can be used on serum or CSF and the sensitivity in CSF is greater than 90% in cryptococcal meningitis. Their sensitivity with blood testing has probably been overstated. The kits have been designed primarily as qualitative diagnostic tests rather than as tools to quantify the amount of antigen present. However, they can be adapted to offer semiquantitative information and there has been interest in using the tests to assess individual patient response to treatment. However it is difficult to ensure consistency between different patient samples, or over time with the same patient, and quantitative cryptococcal antigen measurement has so far proved disappointing as a clinical tool to measure response to treatment (Aberg *et al.* 2000).

Serotyping

There are immunotyping kits to distinguish the various cryptococcal serotypes. However, they are expensive, and currently patient management is more likely to be altered through knowledge of their underlying immune status. Distinction between *var gattii* and other varie-

ties can be satisfactorily determined using biotyping agar.

TREATMENT

Anti-fungal drug options for cryptococcal disease are limited.

Amphotericin B is the mainstay of treatment. This broad spectrum drug is fungicidal and *in vitro* resistance is extremely rare. However, nephrotoxicity is a significant problem, although is usually reversible if the total dose does not exceed 4 g (Khoo *et al.* 1994). It is exacerbated by salt depletion, and it has been suggested that patients should receive a normal saline infusion prior to amphotericin administration. Bioavailability is extremely poor via the oral route and it must be given intravenously. It has curious and poorly understood pharmacokinetics – despite being undetectable in CSF it is effective in cryptococcal meningitis. Amphotericin B causes membrane disruption through binding to sterols in the cell membrane, but it probably also has an effect through stimulating macrophage function. It can be given intrathecally, but this is recommended only as part of salvage therapy for relapsed patients. The lipid formulations of amphotericin B have the advantage of lower toxicities, and can be given in higher dosage of up to 10 mg/kg/day. However, they are considerably more expensive.

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Flucytosine is a nucleotide analogue. Available in oral and intravenous formulations, it appears to have a synergistic action with amphotericin *in vitro* (Schwarz *et al.* 2003). A randomised trial showed a trend towards more rapid CSF sterilization in patients receiving flucytosine in combination with amphotericin compared with amphotericin alone (van der Horst *et al.* 1997). Flucytosine is converted to fluoro-uracil within the fungal cell, and this is the active drug. It has the disadvantages of high

Figure 5 (a) Brown mucoid colonies of *C. neoformans* on birdseed agar and (b) blue discoloration of CGB agar by *C. neoformans* var *gattii*.

Other than the clinical status of the patient and CSF sterilization, there are no satisfactory markers of response to treatment

cost, poor tolerability, rapid development of resistance if used as monotherapy, and the need to monitor blood levels.

The azole drugs (e.g. fluconazole) have revolutionized the treatment of fungal infections because of their potency, tolerability, good CSF penetration, and oral and intravenous formulations. Their mechanism of action is inhibition of sterol synthesis by the fungal cell so they may in theory adversely affect the action of amphotericin if used in combination. This has not been born out in animal studies, and there is now good data emerging from the treatment of systemic candidaemia that this is unlikely to be a problem (Rex *et al.* 2003). There is most experience with fluconazole in the treatment of cryptococcal meningitis. While it is not as potent as itraconazole *in vitro*, it has better CSF penetration and appears more effective in clinical trials (Saag *et al.* 1999). The newer azoles such as voriconazole and posaconazole appear to have better *in vitro* activity against *C. neoformans* than fluconazole, but there are no data from controlled trials in cryptococcal meningitis.

Unfortunately the newer classes of antifungal agents such as caspofungin do not appear to have good activity against *C. neoformans*.

CURRENT TREATMENT GUIDELINES

Treatment guidelines were published for cryptococcal meningitis in 2000 (Saag *et al.* 2000) (Table 3). There are three phases – induction, consolidation and maintenance (also known as secondary prophylaxis). The guidelines are largely based upon conclusions drawn from a double blind multicentre trial published in 1997 (van der Horst *et al.* 1997). This trial

compared amphotericin alone vs. amphotericin combined with flucytosine for the initial 2 weeks of treatment, followed by either fluconazole or itraconazole for 8 weeks. It was not analysed on an intention-to-treat basis and a large number of patients appear to have been lost to follow up. The trial did not show any difference in clinical outcome between the treatment arms. Despite this, the study investigators recommended that amphotericin in combination with flucytosine be the first line treatment for cryptococcal meningitis. While there was a trend towards more rapid CSF sterilization in the combination treatment arm, and there is some *in vitro* evidence from other trials suggesting synergy between amphotericin and flucytosine, in fact the results from this trial were not robust enough to allow the investigators to make this recommendation. There is some evidence that in HIV negative patients the combination of flucytosine with amphotericin is beneficial, but these data relate to a much lower dose of amphotericin (0.3–0.4 mg/kg/day) (Bennett *et al.* 1979). There is no evidence that the combination of flucytosine with higher dose amphotericin is beneficial. Moreover, HIV positive patients are more likely to have adverse drug reactions with most of the antifungal drugs than HIV negative patients. There need to be more treatment trials in cryptococcal meningitis, but with the advent of HAART there is decreasing interest in this disease in industrialized countries.

Once the first two phases of treatment have been completed, patients with HIV infection need to continue on long-term fluconazole maintenance therapy. The dose is 200 mg per

Table 3 Recommended treatment guidelines for cryptococcal meningitis (Saag et al. 2000)

PHASE	DRUG	DOSAGE	DURATION	ADVERSE EFFECTS	ALTERNATIVE
Induction (initial 2 weeks)	Amphotericin B	0.7–1 mg/kg/day iv	At least 2 weeks	Nephrotoxicity	Liposomal amphotericin B
	and Flucytosine	100 mg/kg/day in four divided doses	At least 2 weeks	Rigors and fever during infusion Abdominal pain Vomiting Diarrhoea Marrow suppression	
Consolidation	Fluconazole	400 mg/day	8–10 weeks	Gastrointestinal disturbance, Elevated liver enzymes	Itraconazole 400 mg/day
Maintenance	Fluconazole	200 mg/day	Lifelong. Probably safe to stop after immune reconstitution with HAART		Itraconazole 200 mg bd Thrice weekly amphotericin B

day. The relapse rate with this regime is in the order of 2% per year. An alternative maintenance therapy is intermittent amphotericin, but this is less effective (Powderley 1992). There is increasing evidence that the rise in CD4 count observed with HAART provides meaningful anti-cryptococcal immune reconstitution, and that it is probably safe to stop maintenance therapy once the CD4 count has risen above 100 cells/ μ L (Vibhagool *et al.* 2003). However, if the CD4 count falls below 100 cells/ μ L again, then most physicians would recommend the re-introduction of maintenance therapy.

There are less recent data regarding the optimal treatment of cryptococcal meningitis in non-HIV infected patients. In part this is due to the difficulty in gathering enough patients to perform adequately powered trials. It is not clear whether treatment should differ according to the infecting variety of *Cryptococcus*. Thus treatment recommendations tend to follow those for HIV positive patients. An alternative is to give amphotericin B 1 mg/kg/day for 6–10 weeks, but this has the disadvantage of its inconvenient formulation and nephrotoxicity. If the patients are immunosuppressed they may need to continue maintenance treatment life-long. Without maintenance therapy there is a significant risk of disease relapse of 15–20%, and therefore close follow-up is mandatory.

Other than the clinical status of the patient and CSF sterilization, there are no satisfactory markers of response to treatment. The difficulties in the use of cryptococcal antigen titres have been described above. The interpretation of antigen levels in CSF is further complicated by the fact that the level is a function of the rate of production and removal. Antigen may be present in brain parenchyma and leach into the CSF over some weeks. In HIV-negative patients, persistently high CSF cryptococcal antigen titres are predictive of relapse, but there are no precisely defined titre levels to help guide management decisions. In HIV-positive patients a rise in CSF cryptococcal antigen appears to predict relapse, but is otherwise of little use. Frequent clinical review and CSF examination is recommended.

COMPLICATIONS OF CRYPTOCOCCAL MENINGITIS

Raised intracranial pressure

The commonest complication is raised intracranial pressure (ICP) which occurs in more than

50% of patients (Saag *et al.* 2000). This is probably due to impaired drainage of CSF by polysaccharide capsule. Among HIV-positive patients, a rise in ICP over the first 2 weeks of treatment is associated with a poor clinical response. Careful management of raised ICP is thought to reduce mortality. Current recommendations suggest that this is achieved through physical drainage of CSF, with repeated lumbar puncture, insertion of drains or ventriculo-peritoneal shunting but there have been no large-scale randomised trials of the impact of these interventions. It is not clear how frequently lumbar puncture should be performed for therapeutic drainage. The current recommendations are that lumbar puncture should be performed daily to keep the CSF pressure within the normal range in those patients who have an ICP > 200 mm CSF until the pressure has been normal for several days. Mannitol has not been found to be useful in managing raised ICP. Published guidelines suggest that corticosteroids should be avoided in HIV-positive patients because of their high fungal burden and the potential for further immunosuppression. However, there are no data to confirm these recommendations.

There has also been interest in the use of acetazolamide as a treatment for raised ICP. The most recent controlled trial in HIV patients was stopped because of adverse events, including acidosis, in the active drug arm (Newton *et al.* 2002). However, only a small number of patients had been recruited, and the trial needs to be repeated. It may be that the dose of acetazolamide at 1 g/day was too high.

Visual impairment

Blindness is common in cryptococcal meningitis, particularly in HIV-negative patients (Seaton *et al.* 1997b). It is thought to be due to raised intracranial pressure, direct invasion of the optic nerve, or adhesive arachnoiditis. There are some retrospective data that suggest that corticosteroids may be beneficial in HIV-negative patients with *var gattii* infections in reducing visual morbidity (Seaton *et al.* 1997a). The current treatment guidelines do not recommend their use, but there have been recent trials in bacterial meningitis demonstrating their good safety profile, and a prospective trial is needed.

Cerebral infarction

Cerebral infarction is a recognized event in chronic meningitides such as tuberculous meningitis, and it is also recognized in cryptococcal

meningitis (Lan *et al.* 2001). There is evidence from the murine model of cryptococcal meningitis that the anti-inflammatory fibrinolytic agent pentoxifylline reduces mortality when used in combination with amphotericin B (Ostrosky-Zeichner *et al.* 1996). There are no data on the use of anti-inflammatory drugs in humans with cryptococcosis.

IMMUNE RECONSTITUTION IN HIV RELATED DISEASE

Over the past few years it has been recognized that patients with HIV can develop clinical syndromes, analogous to the paradoxical reactions seen during the treatment of tuberculosis, as they develop immune reconstitution as a result of starting HAART. A small number of cases of apparent immune reconstitution occurring in patients recently treated for cryptococcal meningitis have now been described (Jenny-Avital & Abadi 2002). The cases are usually sterile meningitides, and occurred up to 11 months after initiation of HAART. The clinical difficulty is in distinguishing relapsed disease from the reconstitution syndrome. Consequently the patients were managed with antifungal treatment and continuation of HAART. As for most opportunistic infections, it is not yet clear whether it is better to begin antiretroviral therapy immediately, or to delay until the course of antifungal therapy is established or completed.

PROGNOSIS AND OUTCOME

Cryptococcal meningitis is universally fatal if untreated. With treatment, survival is much improved but the death rate remains significant, with the trials reporting mortality rates of between 5.5 and 46% (Casadevall & Perfect 1998). Drug toxicities are frequent, occurring in up to 60% of patients. The patient's underlying disease is probably the single most important factor determining eventual outcome. Those with malignancy have a poorer prognosis than AIDS patients in industrialized countries because of their older age and the relative difficulty in controlling their underlying disease. There has been inconsistency in the factors identified as poor prognostic indicators, but those thought most likely to predict treatment failure are a high initial CSF opening pressure, high CSF cryptococcal antigen and abnormal mental status at presentation (Casadevall & Perfect 1998).

QUESTIONS FOR THE FUTURE

Given the fact that the overall outcome in this

disease is relatively poor, it follows that there are plenty of research questions that need to be answered. Death occurs through both microbiological failure and the development of complications. Thus further research should attempt to determine the optimal antifungal combination – does flucytosine really add any benefit when higher doses of amphotericin B are used? Is it safe to use even higher doses of amphotericin B, given that renal impairment appears reversible provided the total dose remains below 4 g? Is the combination of amphotericin B with fluconazole tolerable and effective or do the drugs antagonize each other?

There need to be prospective randomised trials of the role of corticosteroids in meningitis in HIV negative and HIV positive patients with clinical outcome measures rather than surrogate outcomes such as CSF sterilization, and of their use in immune reconstitution syndromes in HIV patients. The optimal duration of treatment has not been determined for HIV negative or HIV positive patients. The best method for managing raised intracranial pressure still needs to be determined, and the use of acetazolamide should be investigated further.

CONCLUSIONS

- Cryptococcal meningitis is going to become a larger world health problem as the HIV pandemic continues to grow in the years to come.
- The bulk of this disease will be in the developing world as those in richer countries will be protected by the meaningful immune reconstitution that HAART confers.
- While there are treatment guidelines, there is a lack of good quality evidence using clinical outcomes upon which to base decision-making.
- Mortality remains high for this disease, and more effective antifungal agents are needed.
- Raised intracranial pressure is common and is a poor prognostic factor; therapeutic lumbar drainage is an important part of current treatment.
- The relapse rate is high. Lifelong maintenance therapy with fluconazole is necessary in patients with immunosuppressive conditions, and patients with apparently normal immune function need careful surveillance.
- Controlling the underlying disease that has predisposed a patient to developing cryptococcal meningitis is key in producing a good outcome.

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