Fungal infections in the ICU

W.D. Francois Venter and Ian M. Sanne
Reproductive Health Research Unit and Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa

INTRODUCTION

About 150 species of fungi are recognised as causing disease in humans. Many of these are nuisance infections, affecting the skin, mucosa and subcutaneous tissue. Very few fungi cause serious infections in humans, and before the advent of chemotherapy, immunosuppression, and human immunodeficiency virus (HIV) infection, systemic fungal infections were notably rare. In Africa, systemic fungal diseases have dramatically escalated with the HIV epidemic. Diseases treated as a small numbers of case studies collected over a century, are now part of the daily experiences for patients and clinicians.

Pneumocystis carinii shares morphologic and structural features consistent with protozoa and fungi. For many years, it was regarded as a protozoan by taxonomists. Clinicians were comfortable with the classification, as the disease caused by the organism does not respond to conventional antifungals, principally because the cell membrane lacks ergosterol, on which many antifungals work. However, subsequent analysis of pneumocystis RNA suggests substantial homology with other fungi, and the organism is widely regarded as such (1). Pneumocystis carinii is an important and common cause of disease in Africa, presenting overwhelmingly in HIV-positive people (2, 3).

Human mycoses are generally acquired from the environment. Human-to-human transmission is very rare, although sexual transmission of histoplasmosis is reported. Laboratory acquired infection is documented, and routine infection control procedures should be observed, with particular care taken with histoplasma and coccidioides. Humans are not natural hosts to all but a few isolated species, and infection represents no
selective benefit to the species. Two yeasts, Candida and cryptococcus, represent the vast majority of disease in the tropics (4-6).

**CRYPTOCOCCAL INFECTION**

Despite cryptococcus being isolated in 1894, the disease only became a clinical problem in the 1970’s with the rise of widespread use of immunosuppressive therapies for transplantation, auto-immune diseases and malignancies. The advent of HIV infection produced an even greater explosion of the disease in the 1980’s, and it has become the commonest disseminated fungal infection in this group. HIV infection in Africa brought a wave of cryptococcal disease, specifically cryptococcal meningitis. Blacks seem to be particularly at risk, and the disease appears to be especially prevalent in Southern Africa. Amphotericin B only suppresses the disease, without curing it.

The organism is ubiquitous, able to survive in a variety of ecologies, and cases have been described around the world. The organism is commonly found in soil and bird guano, although whether humans acquire it from these sources is unknown. The organism is rarely found in humans as a commensal, where it usually causes a transient infection.

Two important subgroups of *Cryptococcus neoforms* have been recognised – *gattii*, associated with eucalyptus trees and found in the tropics, but very rarely the cause of disseminated disease in AIDS patients, and *neoformans*, which accounts for almost all clinical disease (7-12).

**Clinical presentation**

The organism is inhaled through the lung in aerosolised form, infects a primary lymph node complex, and then disseminates systemically. The brain has an unexplained susceptibility to infection during systemic spread, but almost all organs have been involved (13).

**Central nervous system infection.** Central nervous system (CNS) infection is the commonest clinical manifestation of cryptococcal infection, usually presenting as meningoencephalitis. The disease rarely mimics classic bacterial meningitis and usually presents with fever, headaches, malaise, nausea, altered mentation, seizures, cranial nerve palsies, and blindness. Symptoms commonly occur over weeks and even months. Cryptococcosis is generally associated with a CD4 cell count
Fungal Infections in the ICU

below 100 cells/ml, in patients with AIDS. In these cases there may be a more rapid progression of symptoms than in those with other forms of immunosuppression. Cryptococcal meningitis is uncommon in HIV-infected children.

Diagnosis is easily made by examination of infected tissue or culture. CSF examination may be remarkably acellular, with a raised protein and low glucose. India ink examination is positive in three quarters of patients, but cryptococcal antigen detection in the CSF is extremely specific and sensitive (14-16).

Pulmonary cryptococcosis. The lung is the second commonest organ affected clinically, although most infections are asymptomatic. Subacute symptoms of cough, fever, and dyspnoea are the usual presenting features. “Allergic” pneumonitis is very uncommon, as is mass-related phenomena. The chest radiograph may demonstrate infiltrates, cavities, nodules, adenopathy, effusions, and masses. Localised pulmonary cryptococcosis is usual in HIV-negative patients, but uncommon in HIV-positive patients. With AIDS patients, concomitant infection with TB, Pneumocystis carinii and other respiratory pathogens is well-described, making diagnosis and successful treatment difficult (17, 18).

Other organs. The organism has been described to infect almost all organ systems. In AIDS patients, the isolation of cryptococcus in a non-central nervous system location usually means there is subclinical infection of the brain.

Treatment

The disease is rarely curable in AIDS patients, much like other diseases such as histoplasmosis and toxoplasmosis, in the absence of antiretroviral therapy. The goal therefore is to aggressively suppress infection until clinical signs have settled, and then to continue suppression.

Amphotericin B is generally indicated for all severe infections as initial therapy, and is probably best therapy for the initial therapy of all AIDS patients. Amphotericin B is very effective, despite a significant side-effect profile. Despite limited penetration beyond the blood-brain barrier, levels are adequate to achieve control of the fungal load in the meningeal space.

Azole therapy with itraconazole or fluconazole is very useful for treatment and prophylaxis of cryptococcal CNS infection. Azole therapy may be
used as first-line therapy in stable patients without CNS involvement. Ketoconazole penetrates the CNS very poorly, and is only effective for infection not involving the meninges in HIV-negative patients. However, fluconazole is generally regarded as the azole of choice, due to its excellent side effect profile, especially compared to ketoconazole.

It is not clear whether combining an azole with amphotericin B is useful in the initial therapy of cryptococcal disease. Complications, such as hydrocephalus, may require surgical intervention (19, 20).

ICU management of this condition should always be considered. Even with AIDS patients, access to antiretrovirals may lead to a dramatic clinical improvement and expanded life span, if the episode of cryptococcus can be managed successfully. CNS cryptococcal disease can completely resolve if treated aggressively. Patients with altered levels of consciousness may require ventilation, while waiting to see the response to amphotericin B. In these cases, repeated spinal taps to reduce intracranial pressure should be considered, especially if prior taps have demonstrated improvement.

Occasionally, a patient may experience immune reconstitution syndrome on starting antiretroviral therapy, with sudden onset of neurological symptoms. A similar clinical response may occasionally be seen with the initiation of fungal infection. It is unclear how best to manage the syndrome – whether to interrupt antiretrovirals and give a course of antifungals, or whether continue antiretrovirals with antifungals, with or without steroids (21-24).

CANDIDIASIS

Candida is another pathogenic organism that has arisen as a major clinical problem in the late 20th century, as a consequence of medical progress. Unlike the other fungi, though, the rise of invasive tissue candidiasis is not linked to the rise in HIV, where it is an uncommon complication (25-28).

Over 200 species of Candida are known, although only a handful is pathogenic in humans. *C. albicans* is the most common isolate in most cases. Isolation of other organisms has implications for drug susceptibility. Candida is the commonest cause of systemic fungaemia in the ICU. In the ICU, medical staff, and especially doctors are an important reservoir of candida infection (29).
Disseminated candidiasis carries a poor prognosis, partly due to delayed diagnosis and the underlying immunosuppression. Diagnosis can be very difficult, as blood, tissue and urine cultures can be negative despite wide dissemination. However, recovery of the organism from blood cultures has significantly improved in the last decade, through a variety of new laboratory methods. Autopsy series suggest that the disseminated candidiasis is seen in neonates, but is otherwise rare in children (30-32).

Candida can thrive in several situations. Bacterial competition in the gastrointestinal tract is frequently decreased through the use of broad-spectrum antibiotics, which have consistently been shown to be a major risk factor for candida. In one analysis, antibiotic use was the single biggest risk factor for candida fungaemia. Interestingly, use of certain antifungal azoles can select for different strains of candida (33). Neutropenia is a major risk factor, with dramatic increases in the candida colony load documented in multiple sites in the body. Cytotoxic therapy, immunosuppressive agents, corticosteroids, open surgical wounds, major trauma, and other immunosuppressive conditions may predispose to invasion, and the widespread use of antibiotics in this situation may promote increases in colony access to the body (34).

Entry is assumed to be via the gut, damaged integument or via vascular access devices. Wounds and burns have been commonly assumed to be risk factors for candidaemia, as integument colonization is common. Fungal endocarditis in intravenous drug addicts is well described, although endophthalmitis, osteoarthritis, and skin lesions also occur. Intravenous drug abusers are thought to be at risk, especially those using contaminated lemon juice to dissolve heroin. Controversy exists as to whether the access device allows colonization of a vascular channel, or whether intravenous solutions or hyperalimentation are colonized prior and during infusion (35).

**Clinical features**
The setting is the most important factor to consider when assessing the possibility of candidaemia. Patients in ICU’s are at much higher risk than other patients – they are by definition severely ill and therefore immunocompromised, broad spectrum antibiotic use is common, prolonged hospital stays, and intravascular and other catheters are commonly in place (36). Presentation is usually of a fever without resolution on antibiotics. However, even fever is not invariable, as
immunosuppression may preclude a normal response. Endophthalmitis is an important clinical clue, but is not invariable (37).

Chest radiographic features of candida are uncommon, and multiple non-specific manifestations, from lymphadenopathy to interstitial patterns (38).

**Treatment of systemic candidiasis**
Most candida isolates are sensitive to amphotericin B, which is favoured as empiric therapy in severely ill patients with suspected fungaemia. However, *C. lusitania* is inherently resistant, and other species can develop resistance. Flucytosine is only available orally, but achieves high distributions into tissues, as well as crossing the blood-brain barrier. It is generally used in conjunction with amphotericin, and its efficacy in systemic candidiasis is not clear, although small studies suggest efficacy. The azoles are generally effective against candida, but there are differences between the different formulations, and a number of small case reports of clinical and microbiological resistance have been reported (39-43).

**ASPERGILLOSIS**

The term “aspergillosis” is used to describe a bewildering array of clinical diseases associated with exposure to the fungus, some of which may cause a patient to present to the ICU.

Aspergillus is principally a problem in Africa as a result of tuberculosis. An aspergilloma in the lung is probably the commonest serious manifestation of the disease in our setting. Damaged lungs, especially when cavitatory disease is present, may be colonized, and a mass of fungus develops. In a minority of patients, this may lead to haemoptysis, occasionally severe, and mortality is related to the extent of the haemoptysis and degree of underlying lung disease. Fungaemia is very rare. Radiographic appearance is characteristic, and the ‘ball’ may move within the cavity with different positioning. Management is difficult, and antifungal therapy is often of limited, if any, benefit. Surgery is advocated for severe or recurrent haemoptysis. Occasionally, a similar pathological process may occur in the sinuses.

Invasive aspergillus is associated with immunocompromise, especially with exposure to corticosteroids and neutropenia. It is a very rare AIDS-
defining disease in HIV-positive patients. Invasive disease usually involves the lungs, although the brain, skin and other tissue involvement may occur. The diagnosis can be very difficult to make, as blood cultures are only occasionally positive. Amphotericin B is effective in very ill patients and itraconazole in those less seriously ill (41-47).

HISTOPLASMOSIS

The USA and Latin America carries the bulk of the burden of histoplasmosis, but the disease is recognised throughout the world. A handful of cases have been seen in Asia and Europe, but cases have been widely reported from central and southern Africa. *H. capsulatum* is known to occur naturally in caves within South Africa, Zimbabwe, and Tanzania and outbreaks amongst spelunkers is well described.

“African histoplasmosis” refers to disease caused by *Histoplasma capsulatum* var. *duboisii*, although var *capsulatum* also causes disease on the continent. In fact, *H. duboisii* is uncommon, with 250 cases described, with most cases confined to cases in central Africa, between 20°N and 10°S. *H. duboisii* tends to affect the lungs less, but causes more bone and mucocutaneous disease. It has distinct pathological features. Treatment is similar to *H. capsulatum*. Despite the dramatic impact of HIV in terms of other fungal infections, descriptions of AIDS-related disseminated *H. duboisii* infection have been few.

Several cases of laboratory-acquired histoplasmosis have been described (48-52).

Acute Pneumonitis

Epidemics of acute pneumonia due to inhalation of large concentrations of histoplasmosis can occur, and can occur in epidemics. Acute pneumonia is very difficult to diagnose unless it occurs in an epidemic, as the disease is very difficult to confirm by histology or culture, with a very wide clinical differential. Histoplasmosis should be suspected if several cases present one to two weeks after a common exposure, often associated with activity that disturbs dust contaminated with bird or bat droppings.

Clinically, the disease causes a range of symptoms, including fever, malaise, chest pain, cough, myalgias, rigors, nausea, loss of appetite, weight loss, and headache – the classic ‘flu-like illness”. Objective clinical signs beyond the signs of hypoxaemia are unusual. Very
occasionally, disease spread to the pericardium can cause pericardial effusions, pericardial tamponade, and constrictive pericarditis. Extension to the mediastinum can cause life-threatening complications, especially if complicated by fibrosing mediastinitis. The chest radiograph is usually abnormal in severe cases, with bilateral pulmonary infiltrates, hilar adenopathy, and pleural effusions. Laboratory workup rarely shows more than a raised white cell count, and mild transaminitis. Biopsy and culture of tissue is almost always negative. Serological tests lack the sensitivity and specificity to make confident diagnoses.

Treatment is supportive, and most cases resolve spontaneously. Occasionally, respiratory support may be necessary. Pericardial and mediastinal disease may require surgery (48-50, 53-55).

**Chronic Pulmonary Histoplasmosis**
This disease occurs predominantly in Caucasians with chronic obstructive pulmonary disease. It may cause or aggravate hypoxia and cor pulmonale, and cavitation may cause life-threatening haemoptysis. The diagnosis is ideally made by culture of the sputum, but this can be very challenging, often requiring bronchoalveolar lavage. Treatment is with itraconazole or ketoconazole, for up to a year. Surgical resection does not help, as recurrence is invariable (53-55).

**Disseminated Histoplasmosis**
Disseminated histoplasmosis is potentially lethal, and has diverse clinical presentations, from weight loss to hepatosplenomegaly to Addisonian crisis. The disease spreads via the lymphatics to regional lymph nodes, and to the reticuloendothelial system. Patients with immunosuppressive conditions form the largest group with this condition, with the rest made up of those at the extremes of age. Disseminated disease commonly affects the reticuloendothelial system in immunocompromised patients, but can also cause pulmonary, mucosal, adrenal, central nervous system, endocarditis, gastrointestinal, and other lesions. Chest radiographs are abnormal in half of the patients, with lymphadenopathy and a military infiltrate, with nodules smaller than those seen in acute pulmonary histoplasmosis. Bone marrow biopsy and culture is very useful in the diagnosis in 75% of cases, but biopsy of other appropriate tissue should be done as necessary. Bronchoalveolar lavage is useful in AIDS patients. Diagnosis should not be delayed while waiting for culture.

Treatment for non-meningeal and mild disease in non-immunosuppressed patients is adequately treated with azole therapy. Amphotericin B is
necessary for more severe disease, and for those who are immunosuppression. Secondary prophylaxis is necessary for AIDS patients, with itraconazole (48,49,53,56-59).

**Histoplasmosis and the ICU**

Several clinical conditions precipitated by histoplasma may cause disease severe enough to warrant admission to an intensive care unit. Hypoxaemia secondary to acute pneumonitis may occasionally require respiratory support. Chronic pulmonary infections may precipitate haemoptysis severe enough to require intervention, and disseminated histoplasmosis can present with specific or multi-organ failure, particularly in AIDS patients (48-50, 53-55).

**Histoplasmosis and AIDS**

Fever and weight loss is the commonest manifestation of disseminated AIDS-related histoplasmosis, and the CD4 cell count is usually less than 100 cells/ml. 10% of cases present in a way similar to septic shock. 70-80% of cases have positive complement fixation or immunodiffusion tests. Urine and serum antigen testing is very sensitive and specific, but not yet generally available. Amphotericin B is the treatment of choice for patients with severe disease or meningeal involvement, but itraconazole is very effective for patients with less severe disease. Itraconazole is very effective as suppressive therapy. Ketoconazole is ineffective, with fluconazole less effective than itraconazole (56-59).

**OTHER FUNGAL INFECTIONS IN THE TROPICS**

**Coccidioidomycosis**

Coccidioidomycosis is almost entirely confined to people from the Americas, and tends to present as a sub-acute pneumonia, which usually resolves spontaneously. The fungus can cause disseminated disease, especially in immunosuppressed patients, and may uncommonly lead to ICU admission. Isolation of the organism from sputum or other tissue specimen culture, or from transbronchial biopsy, is diagnostic. Serology occasionally gives false-negatives, especially in HIV patients. Azole therapy is generally used as first line therapy, unless patients are severely ill, where amphotericin B is preferred (53, 60).
Penicillium marneffei
Penicillium is a rare infection, although more cases are rapidly arising in endemic areas in Asia, where it is AIDS-associated mycosis. Cases associated with brief travel to the area have been described. It presents as a disseminated infection, with weight loss, fever, anaemia, respiratory and cutaneous involvement, and the diagnosis is confirmed by microscopy or culture. Treatment is usually amphotericin B, followed by suppressive therapy with itraconazole (61, 62).

REFERENCES
Fungal Infections in the ICU


Fungal Infections in the ICU


