10 Yeast Infections in Immunocompromised Hosts

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I. Introduction

A number of yeast fungi are pathogenic, but the two genera that contain the most important animal and human pathogens are *Candida* and *Cryptococcus*. In addition, there are a number of other yeasts that have been, more rarely, implicated in disease.

II. Candidiasis

Members of the genus *Candida* cause superficial infections of the skin, nails and mucosal membranes of the gastrointestinal tract and vagina. They can also invade the tissues and cause fungemia and deep-seated infection of the body.

A. Mucosal Candidiasis

Candida albicans is a normal component of the mucocutaneous flora of humans. Other *Candida* species, such as *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and *C. lusitaniae*, are occasionally isolated but are more frequently recovered in immuncompromised patients and in those receiving antifungal therapy. Among the host defenses against mucosal candidiasis, endogenous bacterial flora are an important factor in suppressing proliferation of *Candida* spp. on mucocutaneous surfaces. Cell-mediated immunity (CMI) and mucosal immunity are closely related to inhibit proliferation and germination on mucosal surfaces (Fidel 2005). Epithelial cells of oral cavity have direct anti-*Candida* activity. In addition, during mucosal infection with *Candida*, a large number of pro-inflammatory and immunoregulatory cytokines are generated by epithelial cells. These cytokines may stimulate chemotaxis, phagocytosis and intracellular killing of infiltrating neutrophils as well as functions of CD4+ and CD8+ T-cells (Chauhan et al. 2006). Phagocytes can recognize *Candida* blastoconidia and hyphae by Toll-like receptors (van der Graaf et al. 2005). A potential link between lower levels of certain pro-inflammatory cytokines and susceptibility to oral *C. albicans* infection has been found suggesting involvement of such cytokines in protection (Dongari-Bagtzoglou and Fidel 2005). Antibody of the IgA class also may assume a role in mucosal immunity to *Candida* infections. Mucus and an intact epithelial cell surface appear to provide an additional line of defense to local *Candida* invasion of mucosal surfaces. Abrogation of these mucosal host defenses against *Candida* may lead to proliferation, local invasion and blood-borne dissemination.

The clinical spectrum of mucosal candidiasis includes oropharyngeal, esophageal, epiglottic and vaginal candidiasis (Pankhurst 2005; Spence 2005). Broad-spectrum antibacterial antibiotics, especially third generation cephalosporins and carbapenems (Maraki et al. 1999; Samonis et al. 2006), may lead to mucosal candidiasis by reducing the normal competing bacterial flora. Mucosal

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candidiasis following the administration of antibiotics is often manifested as oral candidiasis or vaginal candidiasis. However, esophageal candidiasis and severe gastrointestinal candidiasis can develop in immunocompromised patients following the administration of broad-spectrum antibiotics.

The natural history of HIV infection has underscored the critical role of intact CMI in contributing to mucosal host defense against *Candida* (Ohmit et al. 2003). Mucosal candidiasis evolves as an early and frequent manifestation of HIV infection (Klein et al. 1984). As a reflection of impaired CMI, oropharyngeal candidiasis developing in an HIV-positive patient carries an ominous prognosis of developing advanced complications of acquired immune deficiency syndrome (AIDS), such as *Pneumocystis jirovecii* pneumonia. Vaginal candidiasis also may be a recurrent debilitating infection in HIV-positive women. As a logical extension of these mucocutaneous manifestations, development of esophageal candidiasis without other predisposing events in a previously asymptomatic HIV-positive patient has been deemed as an AIDS-defining illness (Laine 1994).

Chronic mucocutaneous candidiasis (CMC) is yet another example of the importance of systemic CMI to mucosal host defense against *Candida* (Kirkpatrick 2001). Chronic mucocutaneous candidiasis is a disease identified most frequently in children. Patients with this disease may have severe recurrent episodes of mucocutaneous candidiasis related to impaired CMI recognition, processing, or response to *Candida* antigens. Recently, altered patterns of cytokine production in response to *Candida* spp. with decreased production of some Th1 cytokines and increased levels of interleukin-10 were found (Lilic 2002). The underlying genetic defect remains unknown but studies are in progress addressing the putative role of dendritic cells and pattern recognition receptors in directing cytokine responses.

Systemic and inhalational corticosteroid therapy also may lead to mucosal candidiasis in patients (Buhl 2006). Studies of experimental mucosal candidiasis reveal that parenterally administered corticosteroid therapy leads to a marked increase in esophageal and gastrointestinal candidiasis in comparison to saline-treated controls. Rabbits treated with parenteral corticosteroid have profound depletion of gut-associated lymphoid tissue (GALT; Roy and Walsh 1992). Lymphoid domes and follicles in such animals are considerably reduced in size. The dome epithelial layer is markedly depleted of M cells and lymphocytes, while the follicular B cell and T cell regions are severely involuted, thus indicating the potentially profound effect of systemic corticoseroids on mucosal immunity (Walsh and Pizzo 1992).

Disruption of an intact epithelium is an important component of locally invasive candidiasis, particularly in those patients who are receiving cytotoxic chemotherapy for cancer. This disruption of mucosal integrity permits invasion of *Candida* into the submucosal regions of the alimentary tract, invasion of blood vessels and systemic dissemination.

Mucosal candidiasis often can be treated by topical therapy, such as with nystatin, clotrimazole, or miconazole (Odds 1992). More severe forms of mucosal candidiasis can be treated with fluconazole (Pons et al. 1993), itraconazole (Saag et al. 1999), voriconazole, amphotericin B formulations or echinocandins, caspofungin, micafungin and anidulafungin. The latter drugs are usually more potent in vitro and have a broader spectrum of activity, including activity against fluconazole-resistant *Candida* species and may be used in the management of refractory mucosal candidiasis (Vazquez 2003).

B. Deeply Invasive Candidiasis

Neutrophils, peripheral blood monocytes and macrophages maintain a critical role in host defense against deeply invasive *Candida* infections. Neutrophils and peripheral blood monocytes phagocytose *Candida* blastoconidia and damage the cell walls and cell membranes of blastoconidia, pseudohyphae and hyphae. Macrophages in liver and spleen clear circulating blastoconidia (Kappe et al. 1992). A number of Th1 and Th2 cytokines as well as hemopoietic growth factors modulate the effector functions of these innate immune cells in response to *Candida* spp. (Roilides and Walsh 2004).

Patients who are neutropenic due to cytotoxic chemotherapy or aplastic anemia have a high risk of invasive candidiasis, particularly in the setting of severe mucosal disruption (Maksymiuk et al. 1984). Additional corticosteroid-mediated suppression of phagocytosis of *Candida* by macrophages further increases the risk of deeply invasive candidiasis in neutropenic patients. Preterm

neonates are also susceptible to colonization and infection by *Candida* spp. (Leibovitz 2002).

While the alimentary tract is the putative portal of entry in many patients with deeply invasive candidiasis, vascular catheters afford another site of entry for *Candida*. By passing mucosal host defenses, *Candida* may be introduced directly through the lumen of the catheter into the blood stream. Consistent with this mechanism of entry are the observations of various epidemiological studies which impute central venous catheters as an independent risk factor for fungemia (Lecciones et al. 1992). It has become an important problem in the intensive care unit followed by increased mortality (Ostrosky-Zeichner and Pappas 2006).

Deeply invasive candidiasis may be classified as fungemia, acute disseminated candidiasis, chronic disseminated candidiasis and single-organ candidiasis. Fungemia may be classified as transient or persistent. Acute disseminated candidiasis is characterized by the development of fungemia and tissue-proven candidiasis. Patients with this acute disseminated candidiasis may have hemodynamic instability and septic shock. By comparison, patients with chronic disseminated candidiasis, other-wise known as hepatosplenic candidiasis, present with a more indolent process of infection of the liver, spleen and other tissues. Single-organ infection is usually the result of disseminated candidiasis that becomes clinically overt at a single organ site; e.g., *Candida* osteomyelitis, meningitis, renal candidiasis and endophthalmitis. *Candida* spp. can form biofilms on catheters and other foreign bodies and become extremely resistant to the antifungal action of both drugs and host immune cells. Echinocandins may be more effective than azoles in eradicating *Candida* biofilms from foreign bodies (d'Enfert 2006).

Treatment of deeply invasive candidiasis depends upon the host and severity of infection (Boucher et al. 2004). Uncomplicated fungemia due to susceptible organisms may be treated with fluconazole in non-neutropenic patients and possibly in neutropenic patients. Other patients with fungemia may be treated with conventional or lipid amphotericin B formulations or with echinocandins caspofungin, micafungin and anidulafungin. Removal of central venous catheters is recommended in patients with candidemia if feasible (Lecciones et al. 1992). Chronic disseminated candidiasis can be treated through a variety of strategies utilizing amphotericin B, lipid formulations of amphotericin B, and alternatively with fluconazole (Pappas et al. 2004).

III. Cryptococcosis

In its most commonly encountered form, cryptococcosis is a chronic, wasting, frequently fatal disease, if untreated. It is characterized by a pronounced predilection for the central nervous system (CNS) and is caused by the basidiomycetous yeast *Cryptococcus neoformans*.

There are two varieties of *C. neoformans* causing disease to humans: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gattii*. The two varieties have different geographic distributions. *C. neoformans* var. *gattii* is most often found in tropical or subtropical regions. In addition, the two varieties have different ecological niches: *C. neoformans* var. *neoformans* is found in association with avian habitats, especially pigeons, while the only natural source of *C. neoformans* var. *gattii* so far identified is debris from eucalyptus trees (Kwon-Chung and Bennett 1984).

Impairment of CMI) is the central immunological deficit leading to increased risk of cryptococcosis. Patients, such as those with HIV infection, those receiving corticosteroids and those with lymphoma, have a particularly increased risk due to impaired CMI. Central to host defense against these infections are T-lymphocytes, particularly T-helper cells, which are markedly depleted or functionally altered in patients with HIV infection. Monocytes, activated macrophages and NK cells also have been identified as playing a role in conferring protection against cryptococcosis.

As clinical evidence of the critical role of CMI in host defense against cryptococcosis, meningoencephalitis due to *Cryptococcus neoformans* occurs in approximately 6–13% of HIV-infected adults and approximately 1% of HIV-infected children. By comparison, cryptococcal infections are rarely seen in neutropenic patients or in immunologically competent hosts. With the advent of HAART the incidence of cryptococcal infection in HIV-infected patients has been dramatically reduced (Ruhnke 2004).

Meningoencephalitis, pulmonary infection, fungemia and disseminated infection are the most common patterns of infection due to *Cryptococcus neoformans* (Chuck and Sande 1989; Panther and Sande 1990; Leggiadro et al. 1991; Gonzalez

et al. 1996). Cryptococcal meningoencephalitis in HIV-infected patients often has few clinically overt signs early in the course of infection but may present in some patients with meningismus, photophobia and seizures (Viviani 1992). Fever, headache and altered mental status are the most common manifestations in cryptococcal meningoencephalitis. These symptoms are usually indolent, often evolving over the course of weeks to months. Unlike some other CNS mycoses, such as aspergillosis, cryptococcal meningoencephalitis seldom presents with focal neurological deficits (Walsh et al. 1985). Patients with altered mental status, evidence of increased intracranial pressure (e.g., papilledema), seizures and focal deficits are considered to be at particularly high risk for sudden death due to CNS cryptococcosis. Cutaneous lesions mimicking molluscum contagiosum may develop as a manifestation of disseminated cryptococcosis.

Diagnosis of cryptococcal meningitis in HIV infection can usually be established from cerebrospinal fluid (CSF) by a combination of direct examination on a wet mount, CSF culture and cryptococcal capsular polysaccharide antigen detection in CSF. The organism usually appears as an encapsulated budding yeast. However, infections by some "capsule-deficient" strains have been reported in patients with HIV infection (Bottone and Wormser 1985). These strains may be misdiagnosed upon direct exam as other yeasts or as contaminating particles. The CSF cell count, glucose and protein in patients with HIV infection may be virtually normal, due apparently to the paucity of an effective inflammatory response. Although a CT scan is usually non-specific in most cases of CNS cryptococcosis, the CT scan may reveal hydrocephalus or cryptococcomas. When stained with periodic acid Schiff (PAS) biopsy specimens of suspicious skin lesions may reveal encapsulated budding yeast cells. Mucicarmine or alcian blue stains can be used to specifically stain the mucopolysaccharide capsule.

Several features are more distinctive in cryptococcal meningitis in HIV infection in comparison to other immunocompromised populations, such as those with cancer or organ transplants. The CSF antigen in HIV-infected patients with meningeal involvement tends to be substantially higher, often exceeding 1:1024 in seriously ill patients. Consistent with these serological findings, the concentration of organisms in CSF of patients with HIV infection tends to be substantially higher than that of patients with cryptococcal meningitis who do not have HIV infection; India ink preparation is usually positive in patients with HIV infection and cryptococcal meningitis.

Conventional amphotericin B, 0.5–1.0 mg kg^{-1} day^{-1} or lipid amphotericin B formulations with or without 5-FC for 4–8 weeks is the preferred regimen for the initial treatment of cryptococcal meningitis (Larsen et al. 1990; van der Horst et al. 1997). The role of flucytosine in combination with amphotericin B in HIV infection is controversial, due to dose-dependent suppression of hematopoiesis (Francis and Walsh). Serum concentrations of 5-FC are monitored and maintained at approximately 40 ∝g ml^{-1} in order to avoid this complication. Titers of cryptococcal antigen should decline in the CSF during the course of therapy. The optimal duration of amphotericin B therapy is unclear, but due to toxicity at 2 weeks it should be switched to fluconazole. Maintenance therapy for prevention of recurrence of CNS cryptococcosis is necessary in HIV-infected and other chronically ill patients (Zuger et al. 1986; Dismukes 1993). A controlled trial found that fluconazole (200 mg day^{-1}, PO) was clearly superior to amphotericin B (1 mg kg^{-1} $week^{-1}$, IV) in preventing relapse of cryptococcal meningitis in HIV-infected adults (Powderly et al. 1992). Newer therapies such as interferon-gamma and antibody directed against cryptococcal polysaccharide have been tested in phase I–II trials.

IV. Infections due to *Trichosporon*

Trichosporon spp. during the past two decades have emerged as an infrequent but often lethal opportunistic pathogen in granulocytopenic and corticosteroid-treated patients (Walsh et al. 1990, 1993; Kontoyiannis et al. 2004). *Trichosporon* spp. cause a wide spectrum of conditions, which may be classified as summer-type hypersensitivity pneumonitis, white piedra, mucosal infection and deeply invasive infection, including fungemia, single organ infection and disseminated infection (Walsh et al. 1993).

Trichosporon beigelii was previously thought to be the only species. However, the genus *Trichosporon* has undergone extensive taxonomic reevaluation during last decade. Based on morphological, biochemical and most importantly

ultrastructural and DNA characteristics *T. beigelii* was split into a number of distinct species, including *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. jirovecii*, *T. mucoides* and *T. ovoides* (Gueho et al. 1994). *Trichosporon asahii* appears to be much more common in cases of systemic infections, while other *Trichosporon* species are involved in superficial skin lesions. This section reviews only the role of *Trichosporon* as an opportunistic fungal pathogen causing deep infection, which may be acute (most commonly recognized) or chronic in nature. Fungemia and tissue-proven disseminated infection are the two most frequently encountered patterns of infection due to *T. asahii*, particularly in neutropenic patients and organ transplant recipients.

The most frequent clinical manifestations of acute disseminated *Trichosporon* infection include persistent fever, cutaneous lesions, fungemia, renal dysfunction and pulmonary infiltrates. These clinical manifestations often develop despite administration of empirical amphotericin B in granulocytopenic and other immunosuppressed patients. Biopsy of these cutaneous lesions usually demonstrates hyaline hyphae, blastoconidia and arthroconidia within the dermis. The presence of arthroconidial forms of *Trichosporon* in tissue with the other two morphological forms serves to distinguish *Trichosporon* from other opportunistic yeasts. Cultures of cutaneous biopsy specimens usually yield *T. asahii*. Renal infection is manifest as hematuria, proteinuria, acute renal failure or glomerulonephritis with red blood cell casts. Histopathologically, there is infiltration by hyphae and arthroconidia of the glomeruli and renal tubules. *Trichosporon* pneumonitis is due either to hematogenous involvement or aspiration.

Trichosporon is a basidiomycetous yeast, which expresses cell wall antigens that cross-react with glucuronoxylomannan (GXM) capsular polysaccharide antigens of *C. neoformans* (Walsh et al. 1992; Lyman et al. 1995). The commercially available latex agglutination or enzyme immunoassay tests for *C. neoformans* may support the diagnosis of disseminated *Trichosporon* infection.

Isolates of *T. asahii* may be inhibited but not killed by safely achievable serum concentrations of amphotericin B ($2 \propto g\ ml^{-1}$; Walsh et al. 1990). Amphotericin B is fungicidal only at concentrations greatly exceeding those attainable therapeutically in serum. This resistance to amphotericin B has been associated with the frequently persistent fungemia and fatal outcome of disseminated *Trichosporon* infection in neutropenic patients. In vivo and clinical data now support the use of fluconazole and voriconazole in treatment of *Trichosporon* infections (Walsh et al. 1992). Neutropenic patients with *Trichosporon* infection have been successfully treated with a combination of amphotericin B plus fluconazole. Non-neutropenic patients are treated with either fluconazole or amphotericin B, or both, depending upon severity of infection. GMCS and other cytokines reverse the GXM-induced immunosuppression of neutrophils and monocytes (Lyman et al. 1995). These therapeutic interventions have greatly improved the outcome from a frequently fatal infection to a treatable and survivable one.

V. Infections due to *Blastoschizomyces capitatus*

Cases of *Blastoschizomyces capitatus* (formerly *Trichosporon capitatum*) previously described in North America appeared to be indistinguishable from those of *T. asahii*. However, a review of 12 cases of infection due to *B. capitatus* from the University La Sapienza in Rome demonstrated patterns of infection that are distinct from those of *T. beigelii*. Specifically, four of seven patients with pulmonary infection had mycetoma-like cavitations; eight patients manifested clinical and radiological features of focal hepatic lesions similar to those of hepatic candidiasis; and three patients had clinically evident cerebritis and brain abscesses confirmed postmortem. Nevertheless, persistent fungemia, maculopapular cutaneous lesions and renal impairment similar to those of *Trichosporon* spp. also were observed. Mortality in these patients was approximately 60% (Martino et al. 1990). Another 26 cases were more recently reviewed from Spain (Martino et al. 2004). The outcome for neutropenic patients with *B. capitatus* infection was poor. Rapid removal of the central venous catheter was required for treatment of this rare infection. The preponderance of reported cases of *B. capitatus* have been reported from Western Europe, while most cases of *T. asahii* have been reported from the United States. These differences in geographic distribution and virulence between *T. asahii* and *B. capitatus* remain to be explored.

VI. Infections due to *Malassezia* spp.

Malassezia furfur, a lipophilic yeast, causes tinea versicolor, folliculitis and catheter-associated fungemia (Gueho et al. 1998). It has also been implicated as cause of seborrheic dermatitis. Tinea versicolor is an asymptomatic variably pigmented macular cutaneous lesion, usually distributed along the neck, chest and shoulders. Folliculitis due to *M. furfur* presents as a pruritic, papular to papulosquamous eruption distributed most prominently on the facial and neck areas. In immunocompromised patients, *M. furfur* folliculitis may simulate the lesions of acute disseminated candidiasis. Fungemia due to *M. furfur* has occurred in patients receiving lipid-supplemented total parenteral nutrition (TPN) via central venous catheters (Devlin 2006). The lipid component apparently provides a nutritional medium for the organism to proliferate in the host. A syndrome of acute respiratory failure and thrombocytopenia has been described in infants with *M. furfur* fungemia as a complication of lipid-supplemented TPN (Redline et al. 1985). This respiratory failure is related to the sequestration of *M. furfur* yeasts and lipids in the subendothelial regions of the pulmonary capillary bed. Dissemination to other organ sites, however, is seldom reported. *M. pachydermatis* also has been reported as a cause of fungemia; however, this species does not have the obligatory nutritional requirements for C_{12}–C_{24} lipids that characterize *M. furfur*.

Tinea versicolor may be identified by skin scrapings as a characteristic cluster of blastoconidia and hyphae. Detection of *M. furfur* from blood requires supplementation of agar plates with olive oil or another C_{12}–C_{24} oil to promote growth of this lipophilic yeast. This requirement for lipids may permit *M. furfur* to elude detection in blood cultures in the clinical microbiology laboratory, unless lipids are added to suspicious sub-cultures of blood. Management of this *M. furfur* fungemia requires discontinuing parenteral lipids and removing the catheter. Amphotericin B is the antifungal of choice for suspected cases of fungal infection. Immunocompromised children with *M. furfur* fungemia also may benefit from a course of an antifungal azole, such as fluconazole, itraconazole or voriconazole; however, resistant strains have been reported.

VII. Infections due to Dematiaceous yeasts

Among the dematiaceous yeasts causing infections in humans, the model *Wangiella dermatitidis* has a high propensity for infections of the CNS (Dixon and Polak-Wyss 1991). While some patients with infections due to *W. dermatitidis* have clinically overt immunodeficiencies, many have no apparent immune impairment that would suggest an increased risk for invasive fungal infection. Further implicating the intrinsic virulence of *W. dermatitidis*, immunocompetent mice may be infected with this dematiaceous yeast without administration of immunosuppressive agents. Traumatic inoculation of the skin and soft tissues may be the portal of entry for *W. dermatitidis*. The lungs are seldom infected.

Patients most commonly present with chronic granulomatous cutaneous lesions and/or focal neurologic deficits. Mortality appears to be host-dependent. For example, one study found that younger patients (<20 years) had significantly higher mortality than did older patients. Treatment of infections due to *W. dermatitidis* consists of complete resection of the lesion, where possible, and administration of antifungal chemotherapy. Itraconazole is considered the drug of choice in the treatment of *Wangiella* infections. Voriconazole and posaconazole have consistent in vitro activities. Due to a high propensity for recurrence, long-term follow-up of patients treated for *Wangiella* infections is important (Brandt and Warnock 2003; Revankar 2004).

VIII. Conclusions

Yeast infections are those caused by unicellular fungi that reproduce by budding (blastoconidia) or by arthroconidial formation. There are many such fungi that cause disease to humans but the two genera that contain the largest number of pathogens are *Candida* and *Cryptococcus*.

Candidiasis caused by *Candida* spp. consists of both superficial infections of the skin, nails and mucosal membranes of the gastrointestinal tract and vagina as well as invasive infections such as fungemia and deep-seated infection of the body. *Candida* spp. are commensals of their hosts, and infections are customarily acquired endogenously.

The appearance of the fungus in tissue is that of yeast cells and pseudohyphae, though the hyphal character is absent in *C. glabrata* and much reduced in *C. guilliermondii*.

Cryptococcosis in its most commonly diagnosed clinical form involves the CNS. The etiologic agent *C. neoformans* is an encapsulated yeast that occurs in two varieties: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gatti*. Polysaccharides that comprise the capsule may occur apart from the blastoconidia and detection of them in body fluids is a valuable diagnostic procedure.

There are a number of other yeasts that may cause infections, including *Trichosporon* spp., *Malassezia* spp., *B. capitatis* and the dematiaceous yeasts, such as *W. dermatitidis*. They may cause serious infections in both immunocompetent hosts but especially in immunocompromised patients.

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