Overview of Systemic Fungal Infections

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A steady increase in the frequency of invasive fungal infections has been observed in the past 2 decades, particularly in immunosuppressed patients. In recipients of bone marrow transplants, Candida albicans and Aspergillus fumigatus remain the primary pathogens. In many centers, however, Candida species other than C albicans now predominate, and many cases of aspergillosis are due to species other than A fumigatus. Additionally, heretofore unrecognized and/or uncommon fungal pathogens are beginning to emerge, including Blastoschizomyces capitatus, Fusarium species, Malassezia furfur, and Trichosporon beigelii. These opportunistic fungal pathogens are associated with various localized and disseminated clinical syndromes, and with substantial morbidity and mortality. These established, invasive mycoses, particularly in bone marrow transplant recipients, are the focus of this discussion. [ONCOLOGY 15(Suppl 9):11-14, 2001]

The frequency of invasive fungal infections continues to increase, both in the general population and in immunosuppressed patients (bone marrow transplant [BMT] recipients, patients with severe and prolonged neutropenia). Several factors are responsible for this increase in fungal infections, including increasing numbers of patients with impaired host defenses due to underlying diseases and/or immunosuppressive therapy. The inability to diagnose many invasive fungal infections in a timely manner continues to be a significant problem, and improved diagnostic methods are needed to permit early detection of infection. Despite the availability of several newer antifungal agents, therapy remains suboptimal, and much work remains to be done in defining the roles of established and novel modalities for treatment and prevention of infection.

Risk Factors and Frequency of Infection

Several risk factors account for the increased frequency of invasive fungal infections (Table 1). Moreover, multiple risk factors may be present in the same patient, which further increases risk. The most important risk factor for the development of fungal infection, particularly in patients with hematologic malignancies (with or without BMT), is severe and prolonged neutropenia. Chronic graft-vs-host disease, immunosuppressive therapy, multiple courses of broad-spectrum antibiotic therapy, the presence of vascular access catheters, parenteral nutrition, colonization at multiple sites, and prolonged stay in an intensive care unit are all associated with an increased frequency of invasive fungal infection. Finally, environmental exposure (hospital construction sites, contaminated cooling/heating systems) may also be a significant contributory factor. Prevention strategies, therefore, include the use of rooms equipped with high-efficiency particulate air (HEPA) filters to reduce the risk of environmental exposure.[1,2]

Data from the National Nosocomial Infections Surveillance (NNIS) system have best documented the changing epidemiology of nosocomial infections in US hospitals.[3] These data demonstrate that the rate of nosocomial fungal infections ranges from 2.0 to 3.8 infections per 1,000 hospital discharges from 1980 to 1990, with the proportion of fungal bloodstream infections among all nosocomial bloodstream infections increasing from 5.4% to 9.9%. The most marked increases occurred in surgical services (124%) and medical services (73%), and the rate of nosocomial candidemia increased by approximately 500% in large teaching hospitals, and by 219% and 370% in small teaching hospitals and large nonteaching hospitals, respectively. It is of interest to note that the recently reported Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) data from 49 US hospitals indicate that Candida bloodstream infections were nearly as common in the general hospital wards (43%) as in the intensive care unit (ICU) (57%).[4] In this survey, Candida species were the fourth most common bloodstream pathogen, accounting for 7.6% of infections, with such infections being associated with a crude mortality rate of 40%.

Spectrum of Infection
The most common yeast infection in the BMT setting (and in other neutropenic patients) is candidiasis. Prior to the use of fluconazole prophylaxis, the incidence of invasive candidal infection was between 10% and 20%, and the most common species was *C. albicans*. [5] This has decreased substantially since fluconazole (Diflucan), and more recently itraconazole (Sporanox), has been used for prophylaxis. Many studies have documented the changing epidemiology of *Candida* infections with decreasing isolation rates for *C. albicans*, and increasing isolation rates for other *Candida* species. [6,7]

In a study of 491 episodes of hematogenous candidiasis from the University of Texas M. D. Anderson Cancer Center, 42% of cases were caused by *C. albicans*, 18% by *C. tropicalis*, 17% by *C. parapsilosis*, 11% by *C. glabrata*, and the rest by other *Candida* species. Wide use of fluconazole appeared to be playing a major role in this observed shift. However, a more recent survey from the same institution of the distribution of *Candida* species in pediatric patients with candidemia revealed the same pattern. (Table 2).[7,8] These patients do not receive fluconazole prophylaxis, are housed in a separate unit, and are cared for by staff dedicated to the pediatric unit. While antifungal prophylaxis [particularly with fluconazole] and nosocomial transmission have contributed to the changing epidemiology of infection, these data emphasize that other factors may also be involved. Similarly, although *A. fumigatus* has been the primary *Aspergillus* species, *A. terreus* and other *Aspergillus* species appear to be increasing in frequency. Other less common molds, including *Fusarium* species, the *Zygomycetes*, *Bipolaris* and other dematiaceous fungi, and the yeast *Trichosporon beigelii* are being encountered with increasing frequency. The endemic mycoses (histoplasmosis, blastomycosis, cryptococcosis, coccidioidosis, etc) are seen sporadically in immunocompromised patients.

**Characteristics of Candida Infection**

The clinical spectrum of candidiasis consists of local and systemic infections. Local infections include mucocutaneous candidiasis (thrush, rectal candidiasis), esophagitis, epiglottitis, and urinary tract infection. Among systemic infections, the primary problem confronted in the setting of BMT is acute (hematogenous) dissemination. Chronic systemic (hepatosplenic) candidiasis is now infrequently observed at many institutions with the widespread use of fluconazole prophylaxis and treatment. It is clear now that what was once regarded as transient or benign candidemia [ie, positive culture for *Candida* but no clinical indication of infection (normal temperature, and clinical stability with no cutaneous or other distant lesions or *Candida* at other sites)] should be considered as neither transient nor benign. The potential for dissemination of infection in neutropenic patients in such cases is very high, with an attributable mortality of 35% to 40%; many patients who were labeled with transient/benign candidemia returned after discharge with such distant infections as hepatic or splenic disease, endophthalmitis, and osteomyelitis. Patients with candidemia often require catheter removal, and all require antifungal therapy.

Investigators at M. D. Anderson Cancer Center have distinguished between acute hematogenous candidiasis and the syndrome of chronic systemic candidiasis on the basis of histopathologic findings. [9] The intestinal tract is the most probable focus of dissemination in acute hematogenous candidiasis, and the commonly involved organs include kidney, liver, spleen, pancreas, eyes, skin, and skeletal muscle. Histopathology studies have shown that macroabscess or microabscess formation is characteristic of hematogenous candidiasis in neutropenic patients. Blood cultures are positive in approximately 50% of patients; specific diagnosis can be made in some cases on the basis of biopsy.

In contrast, histopathology studies of hepatic and splenic lesions in chronic systemic candidiasis revealed that the host reaction is granuloma formation, rather than abscess formation. Although disease may be acquired during neutropenia in cases of chronic systemic candidiasis, its manifestations, including fever, elevated alkaline phosphatase, and radiographic findings, are much more pronounced once recovery from neutropenia has occurred. As suggested earlier, chronic systemic candidiasis may now be of primarily historical significance; in cases in which it does occur, the ability to provide long-term treatment after resolution of neutropenia is associated with high response rates.

One of the primary problems in the management of *Candida* infections in neutropenic patients is what has been termed the diagnostic paradox [ie, that approximately 50% of patients with disseminated candidiasis do not have positive blood cultures, while positive cultures from even multiple sites (eg, sputum, stool, urine) may not accurately reflect tissue invasion or represent systemic disease. Radiographic imaging is useful, but positive findings usually occur only when...
disease has become quite advanced. Better diagnostic techniques are needed to improve early detection of candidiasis.

**Characteristics of Aspergillus Infection**

The increased frequency of aspergillosis is likely associated with an increase in numbers of immunosuppressed patients, increasing recognition of disease in patients with AIDS, and more aggressive use of antineoplastic therapy designed to produce maximal antitumor effect. In the transplantation setting, the increase is partly associated with broadened indications for transplantation. Frequencies of aspergillosis differ among institutions; at M. D. Anderson Cancer Center, the incidence of aspergillosis among BMT patients is approximately 10% to 15% per year. Localized infection includes primary cutaneous infection, sinusitis, tracheobronchitis, and aspergilloma. invasive infections include pulmonary aspergillosis, sino-orbital aspergillosis, and disseminated infection, including cerebral aspergillosis. Primary cutaneous aspergillosis can occur at intravenous catheter insertion sites or in association with adhesive cutaneous dressings. Local infection is characterized by progression from local pain to erythema and black eschar formation; histology shows invasion of local blood vessels leading to avascular necrosis (infarction). Treatment with surgical debridement and antifungal therapy may lead to response rates better than those observed for other forms of aspergillosis.[10,11]

The paranasal sinuses are a primary focus of *Aspergillus*, and a frequent site of infection in patients with prolonged neutropenia. Patients who develop disseminated aspergillosis frequently exhibit a focus in the sinuses. Local invasion can cause fever, epistaxis, nasal discharge, and sinus pain and can result in orbital, cerebral, pulmonary, or disseminated disease. Plain radiographs are relatively insensitive in detecting infection. Computed tomography (CT) scans show opacification, fluid collection, and, in more advanced infection, bone erosion. Invasive pulmonary aspergillosis is the disease entity most frequently encountered in BMT patients. Clinical manifestations of such infection include fever, dyspnea, and tachypnea and chest pain, which may be pleuritic; hemoptysis and hypoxemia are occasionally observed, and a pleural friction rub may be present. Although radiographic findings are minimal during early infection, a variety of findings on regular radiographs and CT scans are characteristic of infection. These findings include pleural-based wedge-shaped lesions, nodular densities, halo sign and cavitary lesions with an air crescent sign, and diffuse bilateral infiltrates; pleural effusion is uncommon but may be hemorrhagic when present. Blood cultures in patients with invasive aspergillosis are almost invariably negative; at our institution, less than 1% to 2% of patients with disseminated aspergillosis yield positive blood cultures, compared with approximately 60% to 70% of patients with disseminated *Fusarium* infection. The reason for this variability is poorly understood.

**Emerging Fungal Pathogens**

*Trichosporon beigelli* causes localized and disseminated disease most commonly in patients with leukemia and prolonged neutropenia.[12] The spectrum of infection is similar to that seen with *Candida* species, and the attributable mortality rate is approximately 60% to 70%.[13] Therapy for trichosporosis is suboptimal since the polyenes lack consistent activity against these organisms. Azole antifungal drugs appear to have better activity. *Blastoschizomyces capitatus* (formerly *Trichosporon capitatum* or *Geotrichum capitatum*) is another yeast form that has been recognized as a cause of disseminated disease in neutropenic patients.[14] Among the molds, *Fusarium* species have emerged as important pathogens in neutropenic patients and BMT recipients with chronic GVHD.[15] *Fusarium solani* is the most common species and often causes invasive disease involving multiple sites such as the paranasal sinuses, lungs, skin and soft tissue, muscle, bone, kidneys, liver, spleen, and the central nervous system. The manifestations are often indistinguishable from aspergillosis, with the exception of a much higher frequency of cutaneous lesions and positive blood cultures (75%) with fusariosis. There is no standard or highly effective therapy for fusariosis. Reversal of the original immunological deficit (neutropenia, etc), improves the chances of recovery.

**Summary**

The incidence of invasive fungal infection continues to increase and has an enormous effect on the overall survival of neutropenic and other immunocompromised patients. Methods for early detection, before invasive disease and/or dissemination occur, are vital because response to current
therapeutic modalities is suboptimal. The emergence of newer and more persistent fungal pathogens is a significant problem. The development of novel antifungal agents (newer azoles, echinocandins) and newer formulations of standard agents (lipid formulations of amphotericin B and nystatin; intravenous itraconazole) are giving clinicians newer options, but much work remains to be done in evaluating these agents and establishing their role in the overall management of fungal infections. Infection prevention, and modalities to reverse the underlying immunological deficit(s) or enhance the immune response, need to play a larger role then they currently do in this difficult clinical setting.

References:


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