Fungal Infections in the Immunocompromised Host

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1. Introduction

Candida, Aspergillus, and Mucoraceae are the most common causes of serious fungal infection in granulocytopenic patients, while Cryptococcus neoformans, Histoplasma capsulatum, and Coccidioides immitis are important pathogens in patients with impaired cellular immunity. Infections with less virulent fungi, such as Trichosporon, Fusarium, Alternaria, Pseudallescheria, and dematiaceous fungi, are being recognized more frequently.

Neutrophils, monocytes, and macrophages provide the major host defense against Candida, Aspergillus, and Mucoraceae. Diseases or medications that damage phagocytic cells predispose to infection with these fungi. Rapidly progressive illnesses characterize infections in patients with severe granulocytopenia, while a more indolent course may be seen in those with less profound granulocytopenia or with diseases that impair granulocyte function. Cellular immunity provides the most important defense against C. neoformans, H. capsulatum, and C. immitis. They behave as opportunistic pathogens in patients with defective cellular immunity, causing progressive disseminated disease rather than self-limited pulmonary infections. Helper T cells specific for the invading pathogen elaborate cytokines that arm macrophages to inhibit or kill fungal pathogens. Mucosal, but not systemic, Candida infections also are characteristic of cellular immunodeficiency.

1.1. Fungal Infections in Granulocytopenia

Fungal infections are major causes of morbidity and mortality in granulocytopenic patients. Fungal infections occur less frequently in granulocytopenic patients with solid tumors or lymphoma than with leukemia. Duration of granulocytopenia and use of broad-spectrum antibiotics or corticosteroids are risk factors for invasive fungal disease in these patients.

Candida and Aspergillus account for most of the fungal infections following bone marrow transplantation, while other fungi are increasing in importance. Infections following bone marrow transplantation are classified as those developing before engraftment (up to 30 days) and those in the postengraftment period (day 30 to day 100), with the highest incidence occurring after engraftment. Also, a period of vulnerability exists following transplantation during the interval between loss of native immunity and development of passively transferred immunity from the donor. Pretransplant characteristics including underlying myelodysplastic syndrome and unrelated donor status are risk factors for invasive fungal infection. In the postengraftment period, use of corticosteroids for chronic graft-versus-host disease (GVHD) is a significant factor predisposing to fungal infection.
1.2. Fungal Infections in Organ Transplantation

Serious fungal infection occurs in from 5% of patients following renal transplantation to over 20% following liver transplantation, most presenting within 2 months of transplantation. Risk factors include severe underlying disease, prolonged operative times, extended intensive care unit stays, use of broad-spectrum antibiotics, intense immunosuppression with frequent administration of high-dose pulse corticosteroid therapy, and use of devices that breach skin and mucous membrane barriers. More recent studies have identified additional risk factors for fungal infection following liver transplantation, including pre-transplantation anemia, return to surgery, prolonged use of ciprofloxacin; intra-abdominal bleeding, fulminant hepatitis, cytomegalovirus infection; and creatinine >3 mg/dl, operative time >11 hr, retransplantation and early fungal colonization.

The spectrum of fungal diseases varies during the early versus late time period after organ transplantation. For example, Candida and Aspergillus account for most of the early fungal infections following liver transplantation (Candida, 70%, and Aspergillus, 25%). Impaired phagocytic cell function caused by use of high-dose corticosteroid therapy predisposes to these early infections. Later, chronic low-dose corticosteroids, cyclosporin A, or tacrolimus and mycophenolate mofetil impair cellular immunity, predisposing to mucocutaneous candidiasis and systemic mycoses.

1.3. Fungal Infections in Acquired Immunodeficiency Syndrome

Fungal infections are common in patients with acquired immunodeficiency syndrome (AIDS). Mucocutaneous candidiasis occurs in up to 90% of patients but systemic candidiasis is rare. Cryptococcal meningitis occurs in 5 to 12% of patients, histoplasmosis in 2 to 5%, and coccidioidomycosis in 5% in the southwestern United States. Aspergillosis and infections with Mucoraceae, Pseudallescheria, Alternaria, Blastomyces dermatitidis, Paracoccidioides brasiliensis, and Sporothrix schenckii have been reported.

The incidence and severity of systemic fungal infections increase with progression of HIV infection and reduction in CD4 counts. While mucocutaneous candidiasis may develop in patients with CD4 counts between 200 and 500/µl, most patients have lower counts. Esophagitis occurs after CD4 counts fall below 100 cells/µl. Systemic mycoses usually occur in patients with CD4 counts below 100 (median below 50 cells/µl), and aspergillosis in those with counts below 50 cells/µl, often in conjunction with granulocytopenia or corticosteroid therapy. Although the incidence of mucosal and systemic mycoses has fallen since introduction of highly active antiretroviral therapies, they persist as problems in persons who have not accessed health care, who are nonadherent to therapy, or who have failed antiretroviral therapy.

2. Antifungal Prophylaxis in the Immunocompromised Host

2.1. Prophylaxis in Hematology

A recent meta-analysis evaluating nearly 6000 subjects enrolled in randomized clinical trials has concluded that antifungal prophylaxis with fluconazole, itraconazole, or low-dose amphotericin B has reduced the morbidity and mortality related to fungal infections in neutropenic cancer patients, particularly among those receiving hematopoietic stem cell or bone marrow transplants. While a number of different regimens of antifungal prophylaxis have resulted in reductions in fungal colonization and superficial fungal infections, a more important goal is the prevention of serious life-threatening systemic fungal infections. To date, the greatest benefits of antifungal prophylaxis in reducing systemic fungal infections have been realized in patients following allogeneic or high-risk autologous bone marrow transplantation where significant decreases in Candida albicans infections have been realized. As not all patients receiving chemotherapy for acute leukemia are at high risk for invasive fungal infections, it has been more difficult to demonstrate benefit in this population using antifungal prophylaxis. Most presently available antifungals when used in prophylaxis regimens have significant limitations, including low efficacy, toxicity, drug interactions, and cost. Acknowledging these limitations, antifungal prophylaxis appears to be appropriate at institutions where there is a high incidence of invasive fungal infections in patients expected to be profoundly granulocytopenic for >7 days and for those requiring significant doses of immunosuppressant medications following bone marrow or stem cell transplantation.

2.1.1. Fluconazole

Fluconazole has several advantages over other presently available antifungal agents including its overall safety profile, excellent bioavailability in both oral and intravenous preparations, and minor drug interaction potential. Large placebo-controlled studies have demon-