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FUNGAL INFECTIONS IN FEBRILE NEUTROPENIA: DOES STANDARD AMPHOTERICIN B STILL HAVE A ROLE?

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The incidence of systemic fungal infection has increased steadily over the past three decades, particularly in patients who are immunosuppressed. Major predisposing factors for invasive fungal disease include prolonged and severe neutropenia, impaired T-lymphocyte function, and impairment of the function of macrophages. Today, more than ever before, potent systemic antifungal therapy is a crucial component of the management of the severely immunocompromised host. Candida albicans and Aspergillus spp. have been the predominant fungal pathogens in neutropenic patients. However, the spectrum of fungal infection has widened to include many non-albicans Candida spp., Fusarium spp. Trichosporon spp., the Zygomycetes, and demetiaccous molds. Conventional amphotericin B in desoxycholate has remained the standard of treatment of most life-threatening fungal infections since its introduction in 1955. Although several new antifungals have been and are being developed (azoles, pneumocandins, echinocandins, lipid based polyene preparations, etc) conventional amphotericin B is still considered the treatment of choice for many invasive mycoses.

The advantages associated with conventional amphotericin B include:

• A broad spectrum of activity, which includes Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans, most Candida spp. (except C. lusitaniae) Histoplasma capsulatum, Paracoccidioides brasiliensis, and Sporotrichon spp. It has variable activity against Aspergillus spp. and Zygomycetes, whereas Fusarium, Trichosporon, and Pseudoallescheria boydii are often resistant.

• rapid onset of activity

• fungicidal activity

• paranteral mode of administration, which might be preferable in severely ill patients with systemic or disseminated fungal infections.

The overall usefulness of amphotercin B has been limited by the well-known toxicity associated with it, including infusion related adverse events (chills, fever, nausea, vomiting, thrombophlebitis) and dose-limiting nephrotoxicity.

The newer azoles fluconazole and itraconazole offer reduced toxicity and significant activity in certain specific settings. However, the emergence of resistant species (fluconazole) and erratic absorption (itraconazole) remain significant problems. The three lipid/liposomal preparations of amphotercin B (Abelcet®, Amphotec®, and Ambisome®) are all associated with less toxicity than conventional amphotericin B, but have not been shown to be superior clinically, despite the potential for high-dose therapy, and are all much more expensive than conventional amphotericin B.

Infusion related toxicity associated with the use of amphotericin B can be minimized using various premedication regimens. The most common regimens include diphenylhydramine, a corticosteroid, acetaminophen, and heparin. Saline loading may help reduce nephrotoxicity. The overall toxicity (particularly nephrotoxicity) of amphotericin B is dose dependent. Low dose amphotericin B (0.3-0.5 mg/kg) is frequently not very toxic. However, many alternatives are now available for the common indications of low dose therapy. The increased efficacy of amphotericin B at higher doses (1.0-1.5 mg/kg) is clearly associated with higher rates of dose limiting renal toxicity. Such doses are often necessary in immunosuppressed neutropenic patients.

The following treatment strategies are considered appropriate in neutropenic patients:

• low dose amphotericin B for empiric antifungal therapy (particularly in patients receiving azole prophylaxis) and for infections caused by most Candida spp.

• aggressive, high-dose therapy with amphotericin B in those patients with extensive or poorly responsive disease

• switch to lipid preparations (or alternative/investigational agents) in those patients who do not tolerate high dose, conventional amphotericin B, or those who fail to respond clinically to such therapy.

Although the antifungal armamentarium available to clinicians has expanded considerably in the past decade, and several promising new antifungal agents are currently under evaluation, conventional amphotericin will continue to have a significant role for the foreseeable future.