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# NEW TREATMENT MODALITIES IN FUNGAL INECTIONS

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*Fungal infeksiyonlarda yeni tedavi yaklaşımları.*

The possible presence of fungal infections as a cause of fever in neutropenic patients is a major concern since the incidence of documented invasive fungal infection is reported to constitute around 7% of all febrile episodes. Fungal infections account for 20-30% of the fatal events in patients with acute leukemia. Modern broad-spectrum antibacterial antibiotics and the availability of thrombocyte transfusions have improved the survival of patients, thereby putting the patient at risk for disseminated infections by yeasts and moulds, especially in those who have protracted periods of neutropenia. Furthermore, mucositis facilitating the access of colonizing fungi to the body can be due to cytotoxic agents, irradiation and herpes simplex virus infection which is commonly encountered in immunocompromised patients. The majority of these fungal infections are caused by *Candida* and *Aspergillus* species, although occasionally other fungi like *Phycomycetes, Fusarium* species, and *Trichosporon beigelii* may emerge. The variations between centers are considerable and depend on differences in antitumor regimens, use of central venous catheters, hospital environment such as building works leading to raising of dust, climate, etc. Finally, the apparently increased incidence of fungal infections also may be related to a greater awareness of these infections and better diagnostic facilities. However, an extensive autopsy survey by Bodey and co-workers revealed the presence of *Candida* in 66% and of *Aspergillus* in 30% of cases. Most of these infections were not diagnosed or treated antemortem. The mortality rate of invasive fungal infections varies in major series between 40 and 75% with an average of about 60%. These studies, however, comprise very heterogenous patient populations which have been started on antifungal therapy for various reasons and at different stages of their disease. Even under optimal circumstances the overall successful outcome of a documented invasive fungal infection may not exceed 20% in prolonged granulocytopenia. With an increasing number of granulocytes a response rate of approximately 85% can be anticipated and patients with an underlying disease in complete remission will recover in around 60% of cases. The prognosis of patients with a presumed or probable invasive fungal infection, i.e. signs and symptoms suggestive of a fungus without microbiologic or histologic confirmation, amounts to approximately 70%, whereas the response rate of patients with unexplained fever is only 80% if neutropenia resolves. Diagnostic shortcomings do not only restrict the evaluation of therapeutic interventions, they also hamper the establishment of an early diagnosis.

Early antifungal therapy and clinical awareness of the possibility of an invasive fungal infection remain crucial prerequisites to avoid the confrontation with a stage of infection beyond a reasonable chance to cure. By consequence, treatment is often commenced on an empiric basis, *i.e.* for fever not responding to adequate antibacterial therapy. The perceived need for systemically active antifungals may vary between 10 and 80% in different centers.

In view of its broad spectrum of activity, intravenous amphotericin B, at a dose of 0.5-1.0 mg/kg/day, is considered the standard therapy for granulocytopenic patients suspected to have a pulmonary or disseminated mycosis,but one of the reasons for withholding this drug is the

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objective and subjective toxicity associated with its use in already ill, debilitated patients. The antibiotic activity of amphotericin B results primarily from its interaction with sterols in the cell membranes of eukaryotic cells. Destabilization of the membrane function is manifested as leakage of cations if the injury is minimal and reversible; with the loss of macromolecules such as nucleoproteins, the damage is lethal. Binding of amphotericin B to ergosterol, the cell membrane sterol characteristic of fungi, accounts for antifungal activity. Binding to cholesterol, the membrane-stabilizing sterol characteristic of human cells accounts for toxicity, Many regimens have been suggested to mitigate chills, fever, malaise, headache, nausea or diarrhea. However, there is no proof that antipyretic, analgesic drugs such as paracetamol/acetaminophen are effective; release of histamine has not been shown to be a consequence of administration of amphotericin B, so an antihistamine, apart from the sedative effect, may hardly be helpful. Opiates probably only induce a narcotic state diminishing concern for adverse effects and no controlled studies on antiemetic drugs have been reported. The addition of corticosteroids may blunt the antifungal activity since they are sterols that may bind amphotericin B, rendering it unavailable to interact with ergosterol in fungi. Nephrotoxicity is variable from patient to patient, reversible to some degree, and clearly a function of the total dose. Within minutes after an intravenous injection of amphotericin B, renal blood flow is reduced and the production of urine falls. Nephrotoxicity may be reduced by making certain that the patient is eunatremic. So, the dilemma is obvious: too long a delay while awaiting laboratory or clinical confirmation will result in a high failure rate as indicated above, but, on the other hand, starting early on the grounds of persistent fever alone can lead to over-treatment, which may be an unnecessary burden to the quality of life of many a patient.

A high price and the lack of data on efficacy in comparative, randomized trials are the drawbacks of new amphotericin B formulations such as Ambisome®, Abelcet® and Amphocil® which were introduced to circumvent the amphotercin B related toxicity. Early trials with liposomal amphotericin B in patients with persisting unexplained fever have confirmed the expected differences in the toxicity profile, particularly with previous or concomitant use of cyclosporin, platinum deratives and aminoglycosides. Moreover, there even might be a difference in efficacy in favour of the liposomal formulation in patients treated with amphotericin B for empiric purposes. An explanation for this observation is not immediately obvious, but could be related to a more hesitant coadministration of the aforementioned potentially nephrotoxic drugs, resulting in adequate coverage of possibly life-threatening complications such as Gram-negative sepsis and graft-versus-host disease. Therefore, next to the issue of timing, the question of safety and efficacy of the new amphotericin B formulations is a relevant one because every clinician has to balance the toxicity of conventional amphotericin B against the costs of a new compound. Furthermore, so far no clinical studies have been conducted to compare head-to-head the safety and efficacy of different new amphotericin B formulations.