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PROCEEDINGS ARTICLE

Fungal infections: diagnostic problems and choice of therapy

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Fungi are typically opportunistic pathogens. Formerly, limitations in diagnostic techniques explain why invasive fungal infections are usually detected in a late stage of their development. Therefore, traditional guidelines dictate antifungal treatment for all patients with persisting fever. This is not longer justifiable in view of the potential adverse events and the economical burden associated with the use of the new antifungal drugs in an era with improved diagnostic tools. Amphotericin B has been the drug of choice for invasive fungal infections for more than 30 years. Owing to nephrotoxicity, its use in neutropenic patients has been largely abandoned in favor of a lipid formulation of amphotericin B, of which only liposomal amphotericin B has been scientifically tested in the first-line treatment of aspergillosis. Azoles constitute an acceptable alternative to intravenous amphotericin B for many invasive fungal infections.

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Fungi, notably *Aspergillus* and *Candida* species, are responsible for two-thirds of all superinfections that occur after a bone marrow transplantation.[1] Fungal infections have evolved to be serious threats to the survival of immunocompromised patients. Fungi are very seldom responsible for infections in individuals with an intact immune system.

Fungi are eukaryotic organisms that have a cell membrane with ergosterol as the main component, as well as a cell wall that contains chitin, mannoproteins and β-glucan. Both ergosterol in the cell membrane and β-glucan in the cell wall are potential targets for the major antifungal drugs. Of the infinitive number of fungi on this world, there are only a few that can cause disease in humans, and they are roughly subdivided into yeasts and molds. *Candida* species are part of the commensal flora of the skin and mucosal surfaces, and they may become the prevalent pathogen under the pressures of antimicrobial agents that reduce the coexisting bacterial flora. Spores of molds can be found everywhere, but when they become airborne, they can find their way into the patient's respiratory tract. Under normal circumstances, the intact epithelial surface and the mucociliary barrier repels invasion and/or aspiration of fungal cells and spores, but high doses of cytoreductive agents and intensive irradiation as part of the conditioning regimen not only cause neutropenia, but they also inflict serious damage to the mucosal barrier.[2] Under these circumstances, colonizing microorganisms, such as *Candida*, can gain easy access to the bloodstream. Neutropenia is one of the major factors that predisposes to invasive fungal infections, but prolonged use of even moderate doses of corticosteroids is also at least equally detrimental through both impairment of the T-cell function and alteration of the glucose metabolism.

Timely recognition of systemic fungal disease is important in optimizing treatment outcomes, as early initiation of treatment is a major determinant of treatment success. In spite of a muted inflammatory response, clinical signs and symptoms remain important diagnostic tools next to culturing, imaging techniques and, more recently, serological tests. Although clinical suspicion may suffice to start presumptive antifungal therapy, attempts to confirm the diagnosis are mandatory for the optimal management of these infections. *Aspergillus* accounts for 80–90% of mold infections. Mucormycetes accounts for most of the remainder. In most cases, fever refractory to antibacterial therapy constitutes the first indication of invasive aspergillosis and, less commonly, clinical symptoms that relate to an inflammatory process in the lung or paranasal sinuses, including cough, sputum, hemoptysis, dyspnea, pleuritic pain, rales and pleural friction rub for pneumonia and epistaxis, sinus pain and nasal eschar for sinusitis. If left untreated, pulmonary aspergillosis will disseminate hematogenously. The clinical picture of mucormycosis, fusariosis and other mold infections is not fundamentally different from that seen with aspergillosis. A localized pulmonary infiltrate with or without a pleural effusion displayed on high-resolution computerized tomogram of the chest is usually the first objective sign of invasive aspergillosis. It is noteworthy that a routine chest X-ray should be regarded as obsolete in the search for pulmonary abnormalities in a bone marrow transplant; computed tomography scans are much more sensitive and are thus preferred. Although histopathology and culture remain the cornerstones of diagnosing an invasive fungal infection, serological techniques are clearly gaining acceptance.[3,4]

Galactomannan and β-glucan are products that are derived from the fungal cell membrane and cell wall, respectively, whereas a PCR technique screens for the presence of specific fungal genetic material. Unfortunately, there is no commercially available standardized probe for this very sensitive technique.

Facing the possibility of invasive fungal disease in a bone marrow transplant recipient, the physician has to address two questions: 'when' to treat and 'what' to treat with. Until recently, it was almost impossible to detect an invasive fungal infection in an early stage of development. Hence, both prophylactic and empirical strategies that were designed to enable a timely intervention gained great popularity. Amphotericin B inhalations to prevent colonization of the airways by molds and the prophylactic use of itraconazole and posaconazole did hold promise, but clinical trials have not shown consistent benefits.[5]

Overreliance on an empirical strategy is inevitably linked with unnecessary exposure to expensive and potentially toxic antifungal compounds for many patients who do not need it. Selection of the most suitable strategy should consider at least

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three factors: the use of concurrent drugs with a potential for interference with antifungal agents, the prevalence of invasive fungal infections and the availability of diagnostic tools. Centers with a high incidence of aspergillosis, especially if they do not have access to rapid fungal diagnostics, should consider routine prophylaxis. In centers with a low incidence of aspergillosis, a preemptive approach would suffice, using close surveillance of patients and initiating treatment once evidence of infection is present. A strategy based on increased understanding of the predisposing mechanisms and the use of modern diagnostic tools combines timely intervention and rational use of expensive antifungal drugs.[6]

CONFLICT OF INTEREST

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