Empirical Antifungal Therapy for Persistent Fever in Patients with Neutropenia

Str—I wish to comment on the section of the recently published “Practice Guidelines for the Treatment of Candidiasis” [1] that discussed the use of empirical antifungal therapy for persistently febrile neutropenic patients. While I fully agree that available evidence justifies the use of empirical antifungal therapy for patients with antibiotic-refractory fever and neutropenia, I was surprised to note that fluconazole was not given any consideration for use as a possible therapeutic agent in addition to amphotericin B. It is well known that yeasts (in particular Candida species) are the common fungal pathogens during the early phase of neutropenia and that molds (usually Aspergillus species) are encountered beyond the second week of neutropenia. If so, why should we not consider using fluconazole, a safe agent with good antifungal activity, as empirical therapy in patients at low risk for aspergillosis? To my knowledge, there are at least 4 studies (3 published studies and 1 abstract) [2–5] that show that fluconazole has efficacy equal to that of amphotericin B for the empirical treatment of persistent fever during neutropenia. Viscoli et al. [4] excluded patients at high risk for aspergillosis namely those who had an abnormal finding on chest radiography, those with surveillance cultures that were positive for Aspergillus species, or those with a prior history of aspergillosis—in their randomized trial of fluconazole and amphotericin B with patients who had neutropenia with persistent fever that was unresponsive to antibacterial therapy. The response rates were 75% for fluconazole and 66% for amphotericin B, with a significant difference in the frequency of adverse effects (32% vs. 82%). In a similar study by Winston et al. [3], nearly 70% of patients in both the fluconazole and amphotericin B study groups had a good outcome, whereas the frequency of adverse effects was less among those in the fluconazole group (13% vs. 81%). Regarding the dose, the guidelines state that amphotericin B, 0.5–0.7 mg/kg/d, is a reasonable dosage treatment of possible yeast or mold infection in the empirical setting. Such low dosages of amphotericin B are suboptimal for empirical or definitive therapy for aspergillosis. For example, in the study by Winston et al. [3], in which empirical amphotericin B was given in a dosage of 0.5 mg/kg/d, fungal infections occurred with equal frequency in recipients of fluconazole and amphotericin B; mold infections were seen in 4 fluconazole and 3 amphotericin B recipients. Mortality resulting from fungal disease was similar in both study groups. Although invasive aspergillosis is a difficult entity to treat using any dosage of amphotericin B in this patient population, higher dosages (≥1 mg/kg/d) are generally preferred for the treatment of suspected aspergillosis.

Although they acknowledged that there was a paucity of data, the 1997 “Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever,” published by the Infectious Diseases Society of America, recommended fluconazole as an acceptable alternative to amphotericin B for empirical treatment [6]. These guidelines suggested empirical fluconazole use at institutions where mold infections and drug-resistant Candida species (e.g., Candida krusei, Candida glabrata) are uncommon, especially if the patient does not have symptoms of sinusitis and if there is no radiographic evidence of pulmonary infection. Also, fluconazole is an attractive alternative treatment for patients with renal dysfunction and for those intolerant of amphotericin B. The authors of these guidelines were careful to point out that use of empirical fluconazole would be inappropriate for patients who are receiving the same drug as prophylaxis. Because prophylactic use of fluconazole is widespread, the appropriate time to initiate empirical therapy in patients receiving antifungal prophylaxis is another issue that deserves attention.

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Practice Guidelines for Fungal Infections: A Risk-Guided Approach

Str—We would like to compliment Rex et al. [1] and Stevens et al. [2] for their notable work on the recent practice guidelines for the treatment of candidiasis and aspergillosis. Because these infections occur in both immunocompetent and immunosuppressed hosts, the subject matter is quite broad, and the authors handled it in a comprehensive manner.

It has become apparent in recent years that, although neutropenia is one factor that dictates risk for infection, patients in this group are not equivalent. Risks for fungal infections, treatment algorithms, and outcome are dependent on specific deficits associated with the underlying malignancy, the chemotherapy regimen, and the transplantation procedures. One example is that the risk for infection extends beyond neutropenia for recipients of allogeneic hematopoietic stem cell transplants (HSCT). In the candidiasis guidelines, the risk-guided approach to antifungal prophylaxis is mentioned, but the recommendation does not address the duration of prophylaxis for different hosts. The results of the largest randomized trial in allogeneic HSCT recipients [3] and the long-term follow-up analysis of this trial [4] suggest that prophylaxis that is maintained after engraftment is directly associated with a significant mortality benefit. This mortality benefit is attributed to a prolonged reduction in the incidence of invasive candidal infections [4]. Therefore, antifungal prophylaxis that is maintained beyond the period of neutropenia is beneficial for selected high-risk patients, such as allogeneic HSCT recipients.

Arguably, aspergillosis now has the most impact on the care of patients with cancer. As indicated by Stevens et al. [2], host factors dictate the outcome of this devastating infection. Among high-risk patients, such as allogeneic HSCT recipients, outcome is poor; therefore, more efficient high efficacy particular air (HEPA) filtration has been shown to reduce the incidence of aspergillosis in certain situations [5]. Novel prevention strategies are currently being tested in randomized trials. These include prophylaxis; preemptive therapy on the basis of host immune status (i.e., presence of graft-versus-host disease); and preemptive therapy on the basis of detection of laboratory markers, such as those mentioned in the review (analysis of nucleic acids by means of PCR and galactomannan assay) [2].

The guidelines by Rex et al. [1] and Stevens et al. [2] are the admirable attempts of experts to summarize current knowledge and treatment of candidiasis and aspergillosis in a comprehensive manner. However, a common problem with evidence-based review is the significant lag time between performance of clinical trials and publication of the results. Also, many antifungal studies have been limited by design and analysis that have not adequately considered host-dictated variations in risk and outcome. Because the care of neutropenic patients is so complex, perhaps we would benefit from practice guidelines that are directed to the treatment of hosts, rather than directed to treatment for infections caused by specific microbes.

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Intermittent Antimycobacterial Dosage Correction

Str—While reading the article by Narita et al. [1] regarding the use of rifabutin with protease inhibitors for HIV-infected patients with tuberculosis (TB), I noticed that the authors repeatedly remarked about the administration of anti-TB therapy once every 2 weeks. Clinically, such an infrequent dosage would never be employed. Such a dosage would certainly lead to the development of mycobacterial resistance. I imagine that, in an earlier draft of the manuscript, the authors may have said “bi-weekly,” meaning “twice per week,” and that someone converted this to “once every 2 weeks.” The error appears throughout the Patients and Methods section. I am very concerned that a clinician could misinterpret this study and might even prescribe dosing of such important medication once every 2 weeks to patients with HIV and mycobacterial infections.

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