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EDITORIAL COMMENTARY

Timely Intervention for Invasive Fungal Disease: Should the Road Now Lead to the Laboratory Instead of the Pharmacy?

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(See the article by Cordonnier et al. on pages 1042–51)

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When Pizzo et al. [1] reported the results of their landmark study on the empirical use of amphotericin B for treatment of neutropenic patients with persistent, antibiotics-refractory fever, they did not need statistics. The results perfectly reflected the prevailing perception enunciated by DeGregorio et al. [2] and seemed to provide a rational basis for what became clinical habit. As usual, the things that appear absolutely logical are seldom true. However, it took a considerable length of time before this concept of empirical antifungal treatment showed the first cracks and doubts emerged.

The need for empirical antifungal therapy was distilled into a definition—namely, any fever persisting for 3 or more days despite broad-spectrum antibiotic therapy while the patient was neutropenic. In the meantime, we were presented with 4 large studies that compared the potential of various new antifungal drugs for empirical treatment [3–6]. Each drug vied to attain the label for empirical use, although, in fact, no substantial differences between them were found [7]. Liposomal amphotericin B and caspofungin won their spurs, but voriconazole did not [5]. Thanks to the quirks of statistics, we discovered that the drug with the highest clinical anti-*Aspergillus* activity could not be used for empirical purposes because it did not fulfill the criteria of "noninferiority" [8]. This situation has changed considerably in the past 30 years. High-resolution CT of the chest is known to be superior to the traditional chest radiograph for detection of pulmonary fungal disease [9]. It has also been shown that systematic use of this technique permits earlier diagnosis and treatment and thus better rates of survival [10]. The search for metabolites or cell components of a given fungus, such as specific antigens and DNA, led to some crucial developments, the most important of which was the ELISA test for galactomannan, an antigen present in the *Aspergillus* cell wall [11]. Molecular techniques based on PCR have not yet been validated to a similar extent, but an overview of the developments in the diagnostic field indicates that timely discovery of an incipient invasive fungal infection is becoming feasible [12]. The newer diagnostics offered the potential for an alternative to empirical therapy, one that is commonly referred to as the "preemptive" approach. The seminal article of Maertens et al. [13] showed that, by incorporating these new diagnostic tools into their practice, it was possible to reduce the rates of antifungal therapy use by almost one-half, proving that the principle was feasible. They also proposed a randomized trial of preemptive therapy versus empirical therapy to confirm their findings, which one of us (B.E.d.P.) found not to be a particularly attractive idea [14].

In this issue, Cordonnier et al. [15] report the results of their attempt to address the question of whether a preemptive approach is equally effective as an empirical approach in terms of overall survival. The group chose patients they considered to be at high risk of developing invasive fungal disease but excluded allogeneic stem cell transplant recipients. They anticipated a survival rate of 90% for patients given empirical therapy, and their hypothesis was that preemptive therapy would not prove to be inferior to empirical therapy by >10%. Thus, 228 patients would need to be assigned to each arm to achieve a power of 80% with use of a 1-sided 95% CI. The criteria adopted for starting empirical therapy were persistent fever (>3 days of fever and antibacterial therapy) or recurrent fever. The criteria defined for starting preemptive therapy included clin-

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ical signs and symptoms that might be associated with fungal disease as well as mycological evidence found at any time after 4 days of fever and antibacterial therapy. Mycological evidence included *Aspergillus* colonization and galactomannan antigenemia, defined by an optical density $\geqslant$1.5, rather than the now-current definition based on an optical density $\geqslant$0.5. According to the primary outcome, there was no difference in overall mortality between patients allocated to receive empirical therapy and those allocated to receive preemptive therapy. As expected, most patients in the empirical therapy group were treated because of persistent fever. By contrast, most in the preemptive therapy group started treatment because of pneumonia, and there were more cases of invasive fungal disease due to both *Aspergillus* and *Candida* species in this group. The other indications for preemptive therapy, including septic shock, mucositis, and galactomannan antigenemia, accounted for very few indications. On average, preemptive therapy was started almost 1 week later than empirical therapy, but there were no other essential differences between the 2 treatment groups. Importantly, most of the cases of invasive fungal disease and related deaths occurred among patients given induction chemotherapy instead of consolidation therapy or an autologous hematopoietic stem cell transplant. This likely reflects the fact that the outcome of invasive fungal disease depends not only on timely intervention but also on other factors, including the progression of the underlying disease [16]. On the plus side, many fewer patients in the preemptive therapy group received antifungal therapy, resulting in less toxicity and lower drug costs. In the trial, diagnostics were not applied as early or as vigorously as in the study by Maertens et al. [13], and consequently, Cordonnier et al. [15] were unable to provide the advantage of the early detection of galactomannan that Maertens and colleagues showed. The study by Maertens et al. [13] also obtained autopsy specimens for every fatal case, whereas autopsies were not mentioned in the study by Cordonnier et al. [15].

Cordonnier et al. [15] are to be commended for their perseverance in completing what must have been a daunting undertaking, given the climate of opinion at the time. Their results are intriguing and should help tilt the balance in favor of a more diagnostic-driven approach to management of invasive fungal disease. Yet they seem almost mesmerized by the "noninferiority" of preemptive therapy for patients receiving remission induction therapy, to the extent that they overlook their own observation that this approach is at least perfectly suitable for patients given chemotherapy either for consolidation or to prepare for an autologous stem cell transplantation. They make a plea to investigate preemptive therapy further, and we agree, provided that the trial restricts itself to those patients at highest risk—that is, those receiving remission induction therapy. The diagnostic tools available to us should be used more judiciously in such a trial by screening patients from the moment that chemotherapy is started. A PCR method to detect fungal DNA may also prove to be useful, as suggested by White et al. [17], who found *Aspergillus* DNA in serial blood samples from 6 of 40 patients with possible invasive fungal disease and 8 of 149 patients at risk for invasive fungal disease. In their study among allogeneic stem cell transplant recipients, Hebart et al. [18] detected fungal DNA in almost one-half of their preemptive therapy group. These results suggest that the presence of fungal DNA and galactomannan antigenemia appear earlier than do signs and symptoms of fungal disease and add weight to the supposition that there is a transition from infection to disease with respect to mycosis, as is apparent with viral infections. A formal trial would be necessary to test to clarify the advantages of the optimal use of diagnostics. However, we have doubts about seeking "noninferiority" to empirical therapy since that found in the current trial was very marginal indeed leading to the question of whether "the ball was over or on the line." Rather, it may be more important to compare a diagnostic-driven strategy with prophylaxis as the former, appropriately executed, virtually preempts the need for empirical antifungal therapy. To us, this seems the best way of "giving appropriate drugs to the right person at the proper time" [19, p. 1186]. Whatever the strategy, it is also important not to forget that seeking a diagnosis does not stop with the initiation of therapy because, even for cases with negative findings, tests should be repeated at regular intervals to identify potential cases of emerging invasive fungal disease.

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