Between Over- and Undertreatment of Invasive Fungal Disease

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(See the article by Maertens et al. on pages 1242–50)

BACKGROUND OF EMPIRICAL ANTIFUNGAL THERAPY

Chemotherapy-induced neutropenia has been a hot topic since the mid 1960s, when it became clear that many patients who appeared to benefit from aggressive therapy for their malignancy suddenly died as a result of an overwhelming infection, particularly of infections caused by the gram-negative bacilli Escherichia coli and Pseudomonas aeruginosa and the gram-positive coccus Staphylococcus aureus. Administration of broad-spectrum antibacterial therapy on an empirical basis (i.e., before results of the cultures were available) provided a sensible solution in many cases [1]. This empirical approach was readily adopted, and the search began for the most effective regimen, fueled by the plethora of new broad-spectrum β-lactams produced by pharmaceutical companies. Better antibacterial cover and promising results in the treatment of malignant diseases endorsed further intensification of the antitumor regimens, which was, in turn, accompanied by a rapidly increasing number of other opportunistic infections. Infections due to hitherto harmless commensals, such as the viridans streptococci and coagulase-negative staphylococci, emerged during life, but autopsy studies showed that the fungal disease may have caused the unexplained fever during neutropenia, because more than one-half of the patients who had died of or with an invasive fungal infection had never received any antifungal therapy during life [2]. This observation provided a perfect illustration of inadequate diagnosis of invasive fungal disease at an early stage of development and highlighted the necessity for timely intervention.

Given the undisputed success of empirically administered antibiotics against bacillary infections, it was only a matter of time before this approach was put to the test for invasive fungal disease, and it seemed to work. In 1982, Pizzo et al. [3] described an excessive number of deaths related to fungal disease among 16 patients with persistent fever and neutropenia who received no additional antifungals, compared with 18 patients who were protected by intravenous administration of amphotericin B. These results concurred with the general perception and were widely accepted, even though the small number of patients in the trial did not, in fact, allow any reliable conclusion to be drawn. More importantly, the difference between both arms of the study was accounted for by Candida infection. The European Society for Research and Treatment of Cancer performed a second trial and corroborated Pizzo and colleagues’ findings, and they noted that the benefit of intravenous amphotericin B was most pronounced among patients who had not received prophylaxis with oral amphotericin B or nystatin against Candida infection [4]. The results of these studies were taken as justification for administration of intravenous amphotericin B empirically for persistently febrile neutropenic patients, and the practice soon became the standard of care in many countries. The availability of more antifungal agents was accompanied by trials to identify an antifungal compound more efficacious and safer than amphotericin B deoxycholate [5–8]. Although the drugs tested exhibited a more favorable safety profile than did the polyene, improved efficacy remained at least questionable. One reason was that, although infections with Candida albicans were commonplace in the late 1970s, the introduction of fluconazole for prophylaxis virtually eliminated them [3]. Furthermore, the patient populations recruited to the more-recent empirical studies were at a rather low-risk of developing invasive fungal disease because of the limited number of allogeneic hematopoietic stem cell transplant recipients. Consequently, the incidence of invasive...
fungal disease decreased to <10% after the introduction of fluconazole, requiring a sample size of >1000 patients to detect any benefit of empirical therapy with sufficient statistical power [9, 10]. In addition, application of composite end points with fewer as the principal component does not allow a simple assessment of the genuine antifungal potential of the drugs investigated [5, 7, 8].

INFLUENCE OF IMPROVED DIAGNOSTIC TOOLS

Inconclusive study results, the change in medical practice, and the widespread use of prophylaxis with a shift to Aspergillus species as the predominant pathogens should have prompted a reappraisal of the concept of empirical therapy. However, empirical administration of antifungals for fever refractory to broad-spectrum antbiotic treatment still remains the standard of care. Moreover, for some mysterious reason, it was assumed that polyenes given at suboptimal doses empirically would protect against dissemination of Aspergillus species by eliminating hotbeds of infection. The fear of being confronted with invasive fungal disease that was already beyond cure obviously helped maintain a low threshold for commencement of systemic antifungal therapy in patients considered to belong to a risk group. This apprehensive approach was aided and abetted by the serious limitations surrounding diagnostic techniques for detecting invasive fungal infection in a timely manner. The yield of cultures of blood, sputum, or bronchoalveolar lavage specimens was low; serological testing was unreliable; and invasive procedures were often precluded because of concurrent thrombocytopenia. This situation has now changed considerably. High-resolution CT of the chest proved to be superior to the traditional chest radiograph for detection of pulmonary fungal disease, and it was shown that systematic use of this new technique allowed earlier diagnosis, leading to better survival [11]. The search for metabolites or cell wall components of a given fungus and DNA detection offered promising results. Indeed, the assay for detecting Aspergillus galactomannan, an antigen present in the mold’s cell wall, has been extensively explored for screening pending US Food and Drug Administration approval. Molecular biological 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 [12–14]. Maertens et al. [15] incorporated these new diagnostic tests into a clinical trial of 136 neutropenic episodes involving fever refractory to adequate broad-spectrum antibacterials. Their noncomparative study was designed to explore the feasibility of commencement of antifungal therapy based on diagnostic information as an alternative to the classic empirical approach, in an attempt to reduce the exposure to antifungal agents [15]. The serum galactomannan test (with a positive cutoff level of >0.5), bronchoalveolar lavage, and a high-resolution CT were the basic elements in their diagnostic evaluation. Only patients with a positive test result or a radiological abnormality received intravenous liposomal amphotericin B (5 mg/kg/day). They observed that antifungals were deemed necessary for only 8% of episodes, compared with an estimated 35% in which empirical therapy would have been administered according to the customary rules. Only 1 case of disseminated zygomycosis out of 22 cases of invasive fungal disease remained undetected, and the patient was not given antifungal treatment. The overall mortality rate of 18%, although high, was acceptable for a population with probable invasive fungal disease.

It cannot be denied that timing is of crucial importance in the management of invasive fungal disease, but this does not excuse one from attempting to distinguish more accurately between patients truly in need of antifungal therapy from those who do not need any. Maintaining guidelines that dictate treatment of a population in which >90% of patients do not have invasive fungal disease is not justifiable in view of the potential adverse events and the economic burden associated with the use of the new antifungal drugs. There is also sufficient doubt about the efficacy of empirically administered antifungals to justify the demand for an alternative strategy that employs validated laboratory tests and imaging techniques [16]. The preemptive approach should be capable of identifying patients at risk before disease is manifest at a time when therapy would be maximally effective, and it has been applied successfully for management of cytomegalovirus disease in hematopoietic stem cell transplant recipients [17]. Maertens and colleagues have now proven the efficacy of this principle for managing invasive fungal disease predominantly caused by Aspergillus species. The β-glucan test and panfungal PCR may prove useful in coping with invasive fungal disease caused by pathogens other than Aspergillus species [18, 19].

FUTURE DEVELOPMENTS

Maertens et al. [15] rightly proposed that a randomized trial of preemptive therapy versus empirical therapy should be done to confirm their findings. However, it may be inadvisable to attempt such a trial, because the value of the conventional empirical strategy against Aspergillus species remains controversial and would fuel endless discussions about which antifungal drugs should be used. A more productive approach might be to conduct a well-defined, autopsy-controlled observational study to answer the many remaining questions, such as those about the reliability of the diagnostic tests and possibility of using this preemptive strategy for patients who are not neutropenic.

In any event, persistent febrile neutropenia refractory to antibacterial therapy can no longer be used as a compass to steer antifungal therapy, simply because neutropenia is no longer the only predisposing factor for acquiring invasive fungal disease. Impairment of T cell–mediated
immunity, which inevitably accompanies organ transplantation, and the prolonged use of immunosuppressive agents (for whichever purpose) may well prove to be even more hazardous.

The success of a preemptive strategy depends upon meticulous clinical follow-up of patients with predisposing factors during an episode of treatment-induced immunosuppression, as well as the timely and repeated use of reliable and readily applicable diagnostic tools. This approach to managing invasive fungal disease could completely change the face of antifungal treatment of the immunocompromised patient.

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References