Invasive Aspergillosis in Cancer Patients

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By Alison Freifeld, MD [2]

The incidence of invasive aspergillosis is increasing parallel to the intensity of immunosuppressive and myelosuppressive anticancer treatments. Successful management is linked to an understanding of the epidemiologic trends.

Epidemiologic Trends

Recent large autopsy studies from Germany and Japan have confirmed the increasing incidence of systemic fungal infections. A large proportion of this increase appears to be associated specifically with a rise in *Aspergillus* infections. Among over 8,000 autopsies performed between 1978 and 1992 at the University of Frankfurt, there was a 14-fold increase in the number of invasive aspergillosis cases.[2] Over the same time period, the prevalence of *Candida* infections stabilized or showed a declining trend.

Similarly, a national survey of autopsy cases from Japan performed from 1970 to 1995 also showed a doubling in the frequency of all invasive mycoses over the 25-year period (1.8% to > 3%). After the introduction of fluconazole in 1989, invasive aspergillosis surpassed candidiasis as the most common invasive mycosis in this series, with the highest infection rates found among patients with aplastic syndromes and acute myelogenous leukemia.[3]

Fluconazole (Diflucan), which is widely used in the prophylaxis and treatment of *Candida* infections, has no clinically useful activity against invasive aspergillosis. The improved management of candidiasis by fluconazole may, in fact, have "selected" for a population of patients who avoided or survived invasive candidiasis, only to subsequently develop invasive aspergillosis. Fluconazole use is, therefore, a probable factor in the rise of *Aspergillus* infections among cancer patients.

Additionally, as discussed by Dr. Bow, a substantially greater number of patients undergo and survive cytotoxic and immunosuppressive therapies, putting them at risk for invasive aspergillosis. Indeed, in a recent review of 595 patients with proven or probable invasive aspergillosis, the major risk factors were bone marrow transplantation (32%) and hematologic malignancy (29%).[4]

Diagnostic Difficulties

There are no truly conclusive, rapid, and accurate tests to confirm a diagnosis of invasive *Aspergillus* infection. Therefore, the diagnosis is absolutely dependent upon a high level of clinical suspicion for susceptible patients, as described in Table 1 of Dr. Bow’s article.

The early use of computed tomography (CT) scanning of the chest or magnetic resonance imaging (MRI) of the sinuses can provide strong clinical evidence of infection in the proper host. These tests
should be ordered without hesitation in high-risk transplant or leukemia patients with suspicious clinical findings. Pulmonary CT findings include patchy consolidation, pulmonary nodules, cavitary lesions, or a "crescent" air sign. A "halo" sign is particularly suggestive of aspergillosis in a neutropenic or bone marrow transplant patient.[5] In one investigation, early CT scans performed in febrile neutropenic patients with x-ray infiltrates and probable invasive pulmonary aspergillosis identified halo signs in 92%, thus reducing the time to diagnosis of invasive pulmonary aspergillosis from 7 days to 1 day.[6] Improved response rates (as high as 72%) were documented as a result of the earlier diagnosis and initiation of therapy in this study.

Two serum tests for Aspergillus detection are under investigation: polymerase chain reaction (PCR) detection of fungal DNA, and enzyme-linked immunosorbent assay (ELISA)-based detection of the Aspergillus surface antigen, galactomannan. The latter test is now used extensively in Europe, although it has not been approved by the US Food and Drug Administration. An autopsy-controlled study in hematologic malignancy patients indicated that ELISA was associated with greater than 90% sensitivity and specificity in the early diagnosis of invasive Aspergillus infections, even before clinical or radiographic signs were evident.[7] The predictive value of a single positive galactomannan ELISA remains unclear, however, and serially positive tests may have the greatest diagnostic capabilities.

The utility of weekly serum PCR for Aspergillus DNA was recently evaluated prospectively during 92 neutropenic episodes in leukemia patients who had undergone stem cell transplantation.[8] All patients with ultimately proven invasive fungal infection were found to be PCR positive (100% sensitivity), and a positive test preceded clinical evidence by about 6 days (range: 0 to 14 days), with a specificity of 73%. A particular advantage of PCR diagnosis is the potential for rapidly identifying fungal pathogens to the species level. For example, it will be possible with this technology to distinguish A fumigatus from A terreus, which is relatively resistant to amphotericin B.[9] With the introduction of new antifungal agents that have differing spectra of activity, such species identification becomes increasingly valuable.

**Aspergillus Treatments on the Horizon**

The complete response rate for all patients with aspergillosis receiving amphotericin B alone is only 25%. It is even lower for neutropenic cancer patients.[1,4] There is currently no strong clinical evidence that itraconazole (Sporanox) or liposomal amphotericin preparations are more effective than standard amphotericin B. However, two new groups of antifungal agents that show particular promise will soon become clinically available: the new azoles and the echinocandins.

New azole drugs possessing significant anti-Aspergillus activity include voriconazole, ravuconazole, and posaconazole. The former two agents are related structurally to fluconazole and the latter, to itraconazole. In immunocompromised animal models of pulmonary Aspergillus infection, voriconazole and posaconazole were superior to amphotericin B.[10] Similarly, ravuconazole prevented mortality, cleared Aspergillus antigen from the serum, and eliminated fungal organisms from the tissues of both lethally and sublethally challenged immunosuppressed animals with invasive aspergillosis.[11] There are few published clinical investigations describing the efficacy of these agents, despite the fact that some of them are in phase III trials.

Echinocandins are a completely new class of antifungal agents that act by inhibiting synthesis of critical components of the fungal cell wall. This novel mechanism differs from that of the currently available antifungals such as amphotericin B, nystatin, or azole preparations—all of which target the cell membrane. Since mammalian cells also possess cell membranes, they are subject to the cholesterol-disrupting toxicities associated with these older antifungal agents. Since the echinocandins are specific in targeting the fungal cell wall, their therapeutic index is expected to be favorable.

In an open-label, noncomparative study of patients with invasive aspergillosis who were refractory to or intolerant of amphotericin or azole preparations, half of the 45 evaluable patients responded favorably to caspofungin (Cancidas) given for 1 week or more.[12] Renal abnormalities did not appear to be a significant side effect (< 2%) in patients receiving this agent.
In view of these substantial developments, there may be more hope on the horizon for diagnosing and treating aspergillosis than has previously been held. However, our optimism remains guarded as we await the published results of clinical investigations.

References:
12. Maertens J, Raad I, Sable CA, et al: Multicenter, noncomparative study to evaluate safety and efficacy of caspofungin (CAS) in adults with invasive aspergillosis (IA) refractory (R) or intolerant (I) to amphotericin B (AMB), AMB lipid formulations (lipid AMB), or azoles (abstract 1103). Presented at the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 17-20, 2000.

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