Invasive Aspergillosis in Cancer Patients

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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

Dr. Bow has written a useful article summarizing many aspects of the present state of risk factors, prophylaxis, and prevention of invasive aspergillosis with additional comments about treatment. To amplify some of his points, I will look back over the last 5 years from the perspective of an article I wrote in 1995 for the Annales de Medecine Interne (the French equivalent to the Annals of Internal Medicine).[1] In it, I posed several questions concerning the management of invasive aspergillosis, as follows:

- Do a patient's underlying risk factors alter the diagnostic approach?
- Does treatment differ according to patient group?
- Does the neutrophil count or function influence response?
- Does the rate of progression of invasive aspergillosis affect outcome?
- Does the body organ affected influence outcome?
- Does surgical intervention affect outcome?
- Is susceptibility testing of Aspergillus useful to predict clinical management?

In this brief overview, I will touch on these points and summarize the state of clinical management 5 years later. This is important because the incidence of invasive aspergillosis continues to rise and mortality rates remain high.

Do a Patient's Underlying Risk Factors Alter the Diagnostic Approach?

There have been clear advances in the diagnosis of invasive aspergillosis in the neutropenic leukemic patient. The use of computed tomography (CT) scans during neutropenia has allowed earlier interventions (including surgery and switching of therapy) and better outcomes.[2] Caillot et al in Dijon, France, pioneered the use of systematic CT scanning in patients with febrile neutropenia.[2] This allows recognition of the halo sign (ground glass opacification around a nodule or consolidation) - a particularly useful radiologic feature that is transient and best seen within the first 10 days of invasive aspergillosis during neutropenia. There are both false-positive and false-negative appearances (approximately 3% to 10%), and there may be some difficulty in interpreting thick-slice CT scans because of partial averaging effects.

The other major advance in the diagnosis of invasive aspergillosis in neutropenic/leukemic patient is the use of Aspergillus antigen testing.[3] The antigen test has a sensitivity of 93% and a specificity
of 95% for invasive aspergillosis. Two positive samples are required to define a positive case. This test has allowed earlier diagnoses to be made (5 to 14 days earlier) and has also been a trigger for a CT scan of the chest and/or sinuses. It may be useful in following response to therapy, but that is not entirely clear as of yet.

The CT scan and Aspergillus antigen tests are also useful in allogeneic stem cell transplant patients, but there are issues of timing. In the group that presents with invasive aspergillosis during the early neutropenic phase, these tests perform as they would in leukemic/neutropenic patients. In the later phase with graft-vs-host disease, systematic CT scanning is difficult to implement because of the long periods of time during which the patients are at risk. Likewise, Aspergillus antigen detection may not permit a diagnosis early enough to alter outcome as samples are collected less frequently, particularly as response to treatment of these patients is far from satisfactory.

The other area of progress in the allogeneic stem cell transplant patient, however, is the use of polymerase chain reaction in blood, which was pioneered by the Transplant Group in Tuebingen, Germany.[4] It is not yet clear whether polymerase chain reaction screening adds diagnostically to Aspergillus antigen detection in this population, but it is certainly more labor intensive and expensive. Further research in this area is ongoing.

In other patient groups with invasive aspergillosis, the diagnosis has to be made as it has been for the last 20 years, namely via a mixture of suspicion, imaging, culture, microscopy, and biopsy. There are one or two hints that Aspergillus antibody testing may be useful in the setting of solid-organ transplantation, but the variable tests that have been used and the relatively poor sensitivity and standardization of the relevant antigens emphasizes the need for additional work in this area. The same is true for patients with solid tumors, patients with AIDS, and other less immunocompromised patients who might have invasive aspergillosis.

**Does Treatment Differ According to Patient Group?**

Only two drugs are useful for the treatment of invasive aspergillosis—amphotericin B and itraconazole (Sporanox). Response rates to a lipid-associated amphotericin B are similar to those achieved with standard amphotericin B, but the therapeutic ratio has improved, especially with respect to nephrotoxicity. Randomized studies of oral itraconazole vs intravenous amphotericin B were unsuccessful and thus comparative response rates can only be estimates. The response rate to amphotericin B varies from approximately 1% (cerebral aspergillosis in immunocompromised patients) to 60% to 80% in heart and renal transplant patients with pulmonary or cutaneous infection. Collected series suggest an overall response rate of approximately 35%.[5,6]

Response rates to itraconazole appear to be approximately 40% to 60%, again with a wide range in different patient groups and different settings. Fewer data are available on the efficacy of itraconazole than on amphotericin B in more immunocompromised settings (such as allogeneic bone marrow transplant patients) and persistently neutropenic patients, although the drug may be effective in these settings. It is well known that response rates to amphotericin B do not exceed 15% in these difficult situations. Patients who fail amphotericin B may respond to itraconazole and the reverse is also true.[2]

High doses of itraconazole (800 mg daily) may be helpful for cerebral aspergillosis[7] but there are few data to support this strategy. Loading doses of itraconazole are important in patients with rapidly progressive disease. The recent introduction of IV itraconazole provides an alternative option for these patients, but a small percentage of patients may have inadequate concentrations. There are numerous drug interactions with itraconazole. A serum itraconazole concentration of > 500 µg/mL seems to be important.[8]

Sinus aspergillosis responds better to amphotericin B than to itraconazole,[9] and airways aspergillosis may respond better to itraconazole than to amphotericin B. Responses in other sites of disease appear to be similar with both drugs.

**Does the Neutrophil Count or Function Influence Response?**
Patients with persistent profound neutropenia rarely survive. This is exemplified by patients with aplastic anemia in whom the mortality rate is around 90%.[10] Occasionally patients with neutrophil counts in the range of 100 to 500 × 10^6/L have survived for several weeks, but those with essentially no neutrophils rarely do.

Patients with neutrophil dysfunction such as those with chronic granulomatous disease, HIV infection, and diabetes tend to suffer from subacute or even chronic aspergillosis rather than acute disease. Responses to therapy tend to be slow and incomplete, and the relapse rate high.

**Does the Rate of Progression of Invasive Aspergillosis Affect Outcome?**

The answer to this question is clearly yes. Allogeneic stem cell recipients with graft-vs-host disease often present with disseminated invasive aspergillosis and progress rapidly to death. Judging the pace of infection can be difficult as this depends on when the diagnosis is first established. It is now abundantly clear that early diagnosis improves outcome in those with reversible immunosuppression and that this is particularly true in the most immunocompromised patients. Additionally, the cumulative corticosteroid dose is an important factor in survival as demonstrated in allogeneic stem cell recipients.[11]

**Does the Affected Body Organ Influence Outcome?**

In terms of outcome from invasive aspergillosis, there is a hierarchy of sites. The worst site to be affected is the brain, followed by pulmonary disease. Dissemination to other organs may be better or worse than pulmonary disease, depending on whether the skin is involved. Patients with skin disease appear to do particularly well for reasons that are still unclear. There is also a range of responses in patients with pulmonary disease, in which those with extensive bilateral disease do poorly and those with a single small focal area of disease do well. This partly reflects early diagnosis but also underlines immune response. An identical picture was seen in AIDS patients with coccidioidomycosis—the mortality rate among patients with bilateral disease was 70% and for focal disease, it was 30%.[12]

**Does Surgical Intervention Affect Outcome?**

No randomized studies of surgery have been conducted. In fact, conducting such studies would be met with considerable difficulty due to complicating variables. Retrospective analysis of the role of surgery in pulmonary mucormycosis showed a substantially higher survival rate.[13] A consensus has been reached on three indications for surgical intervention in pulmonary invasive aspergillosis. They are (1) in the immediate management of patients with disease abutting on the mediastinum; (2) in those with life-threatening hemoptysis; and (3) as a debulking procedure, particularly in those going on to transplantation. Complications from thoracic surgery in the context of profound neutropenia and thrombocytopenia appear to be minimal.[14]

Surgery also appears to be essential for patients with endocarditis, renal disease, and in making a diagnosis in unusual settings. Hemorrhage and infection is a significant postoperative problem in those with sinus aspergillosis who will be undergoing major surgery during neutropenia.[5] However, the role of surgery in cerebral aspergillosis, Aspergillus empyema, epidural abscesses, and osteomyelitis remains to be determined.

**Is Susceptibility Testing of *Aspergillus* Useful to Clinical Management?**

Successful testing methodology has advanced substantially in the last 5 years. Resistance in *A. fumigatus* has been described in the literature,[15-17] and is present in many different countries. However, the frequency of resistance to itraconazole appears to be low—possibly 1% to 3%. Optimal methods for testing susceptibility to *Aspergillus* have yet to be agreed upon, although numerous methods do detect resistance. Most isolates resistant to itraconazole are not resistant to the new azoles.

Amphotericin B resistance appears to be universal in *A. terreus*.[18,19] Some amphotericin B-resistant isolates of *A. fumigatus* and *A. flavus* have been identified, as defined by extremely poor
responses in animal models, but a testing methodology for use in the typical microbiology laboratory has yet to be developed.

In summary, significant advances have been made in invasive aspergillosis over the last 5 years. The introduction of active new drugs such as caspofungin, voriconazole, and posaconazole should help reduce mortality. Defining the optimal primary therapy regimen and early diagnosis remain priorities.

References:


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