High Mortality in Invasive Aspergillosis: What We Need to Know for Determination of Poor Prognosis and Next Countermeasures

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(See the article by Nivoix et al. on pages 1176–84)

Two major articles that provide definitions and guidelines regarding invasive aspergillosis (IA) have recently been published in *Clinical Infectious Diseases* [1, 2]. These definitions and guidelines were updated from their previous versions, which were published in 2002 and 2000, respectively. Such frequent updates (occurring within 8 years) are required because of the complexity of aspergillosis and the introduction of newer anti-*Aspergillus* drugs, such as voriconazole, echinocandins, and lipid formulations of amphotericin B. These changes also mean that there has been an evolution in the techniques used for the precise and rapid diagnosis of aspergillosis and that newer data are available to inform treatment decisions, although the pace of change has been gradual.

Infectious diseases are simple in principle and involve a host, a microorganism, and a route of infection. Invasive fungal infections (IFIs), however, are rarely simple, with numerous complicating factors

that include: (1) complex immunodeficiencies caused by underlying hematological malignancy, the use of intensive chemotherapy (including immunosuppressive agents and corticosteroids), plus the patient's comorbid condition(s); (2) a lack of specific symptoms and signs of IFI, and (3) difficulty in isolating the pathogen, including *Aspergillus* species, or detecting their specific antigen, such as galactomannan and β-D-glucan, in clinical samples that include blood and bronchoalveolar lavage fluid. Although the major aim of establishing revised definitions of invasive fungal disease was to facilitate the identification of reasonably homogeneous groups of patients, with the goal being to perform appropriate clinical trials and to help communication between international clinicians and researchers [1], such revised definitions also reflect the evolution of diagnostic tools and of our understanding of IFI. The galactomannan and β-D-glucan tests have been extensively investigated for decades as a means of enhancing the reliability of IA diagnosis [3, 4]. In another approach, high-resolution CT has also proven to be a valuable tool [5]. However, no straightforward or exceptional tools exist for the accurate diagnosis of IA. In addition, unraveling all of the fac-

tors associated with mortality in IA is quite difficult.

In this issue of *Clinical Infectious Diseases,* Nivoix et al. [6] have attempted to discover the factors associated with overall and attributable mortality in IA. This study analyzed the complexity of 289 aspergillosis cases. The prognostic factors identified in this analysis as correlates of overall mortality were (1) receipt of allogeneic hematopoietic stem cell or solid-organ transplantation, (2) progression of underlying malignancy, (3) prior respiratory disease, (4) receipt of corticosteroid therapy, (5) renal impairment, (6) low monocyte count, (7) dissemination of aspergillosis, (8) diffuse pulmonary lesions, (9) pleural effusion, and (10) proven or probable (as opposed to possible) aspergillosis. Similar factors also predicted an increased attributable mortality, with the following exceptions: pleural effusion and monocyte count had no impact, whereas neutropenia was associated with a higher attributable mortality.

Although the host factors in definitions of IFI are not actual risk factors for IA, allogeneic hematopoietic stem cell transplantation, receipt of corticosteroid therapy, and neutropenia often overlap. These data suggested that using these host factors in the definition of IFI [1] is relatively appropriate. Other factors, such as the

progression of underlying malignancy, prior respiratory disease, renal impairment, low monocyte count, disseminated aspergillosis, and extended pulmonary lesions are easily understood to affect to the prognosis of IA. However, more-detailed information, such as what kinds of prior respiratory disease affect the prognosis of IA, is worth knowing. Needless to say, early administration of antifungal drugs is extremely important for improving the prognosis of IA [7]. The predicted prognostic factors evaluated in this study [6] will be very useful, not only for estimating the prognosis, but also for making a decision about the early administration of antifungal drugs. However, some caution is warranted. The previous definition of IFI, described by Stevens et al. [8], was applied in the study by Nivoix et al. [6], in which a total of 94 cases were classified as possible cases. Possible cases are usually excluded in clinical trails, because infection by *Aspergillus* species is not highly likely. The inclusion of possible cases by Nivoix et al. [6] makes it difficult to evaluate the true risk factors associated with mortality due to *Aspergillus* infection. In actual clinical settings, unlike in clinical trials for drug registration, physicians use all of the mycological tests, including direct culture and microscopy, as well as indirect serum tests, with the realization that they do not work perfectly (as mentioned earlier). We may wish to treat a possible case of IA to avoid overlooking a potentially fatal disease in a high-risk patient. If we are to avoid excessive preemptive or empirical treatment, it is very important to improve diagnosis and to fill the gap between the definitions of probable and possible cases. It is even better for clinicians to identify which factors are important in distinguishing possible cases from probable or proven cases. Although no such information is provided in this study [6], future research will answer these questions and will hopefully lead to an improvement in the prognosis of IA.

Another novel finding of the study by Nivoix et al. [6] is that the availability of treatment with voriconazole, compared with treatment using other antifungal drugs, has improved the prognosis of IA. The superiority of voriconazole to amphotericin B for the treatment of IA has been already reported [9], and the data in this study [6] provided almost the same result. However, one should recognize that it is not only the newer drugs that have affected the prognosis of IA over the course of this long study period, but that other advances in medical care have also had an impact. It might be obvious that newer agents and a better treatment strategy would definitely affect the prognosis, not only for aspergillosis, but also for all other infectious diseases; however, to be scientifically valid, the results must be evaluated by clinical trials that are strictly designed to compare the effectiveness of the drugs. In this study [6], the clinical backgrounds of the patients were varied, as the authors point out, and one should take into account one notable part of their data: the 12-week overall survival among patients receiving various antifungal drugs was only 52.3%, which is ∼20% less than that reported in clinical trials performed in a more rigorous manner [9, 10]. The authors explained that the reason for this discrepancy was that their study, compared with clinical trials, included a greater number of patients with severe illness, such as patients with renal impairment and/or intubation. This meant that IA was associated with a gross survival rate of 52.3% in actual clinical settings, which reminds us that we need better antifungal drugs. Perhaps the newer antifungal drugs that have recently become available will improve the prognosis of IA. A strong and reliable anti-*Aspergillus* drug is not yet fully available, and we need advances in this field. Because current available antifungal drugs are limited, the possibility of improving the prognosis of IA may depend on the administration of combination antifungal drugs and/or on earlier administration. Combination therapy, although widely discussed around the world, has never been evaluated in a large-scale randomized controlled trial, although such a study is in progress [11]. The latest treatment guideline for aspergillosis does not recommend combination therapy as primary therapy. Results of a combination trial are eagerly awaited. On the other hand, rapid and accurate diagnosis that will enable the initiation of intensive treatment is also important.

In conclusion, Nivoix et al. [6] have identified the important factors associated with overall and attributable mortality in IA. In doing so, they have raised the issue of when it is appropriate to start preemptive therapy. The basic strategy for treating infectious diseases—giving appropriate drugs to the right person at the proper time—remains a prime mandate.

Acknowledgments

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