Counterpoint: Invasive Aspergillosis and the Environment—Rethinking Our Approach to Prevention

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Preventive measures are important in the control of invasive aspergillosis (IA) because diagnosis is difficult and the outcome of treatment is poor. If effective strategies are to be devised, it will be essential to have a clearer understanding of the sources and routes of transmission of Aspergillus species. Nosocomial outbreaks of IA highlight the fact that Aspergillus spores are common in the hospital environment. However, in general, such outbreaks are uncommon. Most cases of IA are sporadic in nature, and many of them are now being acquired outside of the hospital setting. Housing patients in high-energy particulate air–filtered hospital rooms helps prevent IA, but it is feasible and cost-effective only for the highest-risk groups and for limited periods. Control measures, which are designed to protect patients from exposure to spores outside the hospital, are even more difficult. Nevertheless, now that high-risk patients are spending more time outside of the hospital, the cost benefits of antifungal prophylaxis and other preventive measures require careful evaluation.

Invasive aspergillosis (IA) is an increasing problem among immunocompromised patients, affecting \(\leq 14\%\) of lung transplant recipients [1] and \(\leq 28\%\) of patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT) [2, 3]. Because the diagnosis of this infection is so difficult, and because the outcome of treatment is so dismal, preventive measures are of great importance in the control of this disease. It is well recognized that some immunocompromised patients are at much greater risk of developing invasive fungal infection than are others. The likelihood of IA developing in one of these individuals depends on a number of host factors, the most important of which include profound and prolonged granulocytopenia, graft-versus-host disease, and/or rejection of a transplant. In addition to host factors, environmental factors are important in the development of invasive fungal infection. If we are to devise effective measures to reduce the incidence of IA among high-risk patients, it will be essential to have a clearer understanding of the sources and routes of transmission of the etiologic agents of this infection. The recent finding that hospital water is often contaminated with Aspergillus fumigatus is clearly an important one, and it has potential implications for the prevention of human disease [4–6]. Nonetheless, this finding needs to be assessed in the light of other evidence regarding the role of the environment in the development of aspergillosis.

TO WHAT EXTENT IS ASPERGILLOSIS A NOSOCOMIAL INFECTION?

Much of our current understanding about the transmission of IA is based on information gathered from outbreak investigations. Nosocomial outbreaks of IA have become a well-recognized complication of construction or renovation work in or near hospital wards in which high-risk patients are housed [7–11]. These reports have highlighted the fact that hospital air is often contaminated with Aspergillus spores, and they have contributed to the current perception that most cases of IA in immunocompromised persons are hospital acquired. Despite the fact that most hospital out-
breaks of IA go unpublished, it is clear that these events, in general, are uncommon and represent only a small proportion of the overall burden of *Aspergillus* infection.

Most cases of IA are sporadic in nature, and it is much more difficult to determine whether these infections are acquired inside or outside of the hospital setting. There are several reasons for this, but the most important is that the incubation period is unknown. Therefore, any attempt to ascertain the extent to which the disease is hospital acquired must be based on an arbitrary definition. There is, as yet, no agreement as to how to define a nosocomial case of IA, and different authors have adopted different standards. Patterson et al. [12] defined a nosocomial case of the disease as one that occurred >1 week after admission to the hospital or <2 weeks after discharge. On this basis, no fewer than 70% of IA cases diagnosed during a 2-year period of hospital construction were acquired outside of the hospital setting [12]. Furthermore, none of the hospital-acquired cases occurred in wards that were adjacent to the areas where building work was ongoing.

There is other evidence that a significant number of sporadic cases of IA are acquired outside of the hospital setting. In the 1970s and 1980s, most cases of IA among patients with leukemia and among bone marrow transplant recipients occurred during the first few weeks after transplantation, before engraftment had occurred or while individuals were undergoing intensive remission induction treatment. Housing these patients who have granulocytopenia in laminar airflow rooms supplied with high-energy particulate air (HEPA)-filtered air reduced the incidence of IA [11, 13], but sporadic cases of the disease continued to occur. In some instances, the infection was probably hospital acquired (e.g., because patients had been removed from the protected environment to undergo investigations), but in others, the short time interval between admission and infection suggests that the patients were colonized with *Aspergillus* before they entered the hospital. More recently, there have been reports that sporadic cases of IA often develop weeks or even months after persons who have undergone allogeneic HSCT have been discharged from the hospital, long after the granulocyte count has recovered [2, 3, 14–16]. Many of these cases of IA have been associated with acute or chronic graft-versus-host disease and its treatment. In 10 (58%) of the 17 cases of IA reported by Williamson et al. [3], the fungal infection was diagnosed >3 months after unrelated donor transplantation. In another recent report, 21% of patients who underwent transplantation from 1993 through 1999 developed aspergillosis >6 months after HSCT, compared with 4% of patients who underwent transplantation in the same hospital from 1987 to 1993 [16].

Taken as a whole, these studies suggest that a significant number of sporadic *Aspergillus* infections are acquired while individuals are being managed on an outpatient basis. If the incidence of IA is to be reduced, it is clearly of some importance to determine which are the most important sources of infection in both the hospital and the home environment and to develop the most appropriate control measures for these different settings.

**WHAT IS THE SOURCE OF ASPERGILLUS INFECTION?**

The available evidence suggests that IA can be acquired after a wide range of exposures inside or outside of the hospital environment. Because 90% of cases of IA either start in, or are confined to, the lungs, and because *Aspergillus* spores are commonly found in indoor and outdoor air, inhalation is thought to be the usual route of infection. Possible environmental sources of these spores include the soil, decomposing plant matter, household dust, building materials, ornamental plants, flower arrangements, items of food, and water [17, 18]. The relative importance of these various sources is very difficult to determine, particularly for sporadic cases of IA. Furthermore, the mechanisms of transmission during outbreaks of IA may be very different from those involved in sporadic disease.

The evidence incriminating particular environmental sources of *Aspergillus* infection has always been circumstantial. Only a few studies have tried to establish a correlation between the concentration of *Aspergillus* spores in the outdoor and/or indoor air and the risk of human disease or colonization. In one prospective study, monthly environmental cultures were performed during a 6-year period [19]. An increase in the mean concentration of *A. fumigatus* and *Aspergillus flavus* spores from <0.2 to >1 per cubic meter of hospital air was accompanied by a 4-fold increase in the incidence of IA, from 0.3% to 1.2%, in immunocompromised patients. In another study, however, the occurrence of 6 sporadic cases of IA could not be linked to changes in the concentrations of airborne *Aspergillus* spores during a 12-month period with weekly air sampling of hospital rooms in which high-risk patients were housed [20]. The fact that 5 of the 6 IA cases occurred in 1 ward is more likely to have been due to the more intensive cancer treatment regimens administered to patients in that ward than to increased exposure to *Aspergillus* spores.

The best evidence for the role of contaminated air as a source of *Aspergillus* infection comes from the temporal association between some hospital-based outbreaks of IA and periods of construction or renovation in or near the wards in which infected patients were housed [7–11]. Although spores released into the air as a result of building work might sometimes be the source of human infections, nearly all of the published outbreak investigations that have attempted to associate cases of IA with the environmental isolation of *Aspergillus* have used only speciation in their comparisons. In light of the almost universal...
presence of certain Aspergillus species in the hospital environment, this is almost meaningless. Moreover, environmental sampling is often not done until after an increase in the incidence of IA is detected. Thus, there are often no data available on the baseline concentrations of Aspergillus spores to determine whether a cluster of human infections is associated with increased exposure. If the source of the exposure appears obvious at the outset of an outbreak investigation, it is possible that new and unsuspected sources or routes of infection may be overlooked.

It might be supposed that tracing the sources of Aspergillus infections has become less difficult with the advent of reliable molecular typing methods, which are designed to determine the relatedness of particular subspecific strains. Often, however, it is not possible to demonstrate a correlation between patient and environmental isolates [21] and, on the rare occasions that some patient and environmental isolates have been shown to be identical, not all of the patient isolates could be matched with those from the environment [22–25]. In most of these studies, isolates of A. fumigatus from some of the patients with IA were found to be similar to environmental hospital isolates, but no attempt was made to compare these strains with isolates recovered from the patients’ home environments. The failure to detect genetic relatedness between patient and environmental isolates is due, at least in part, to the fact that environmental sampling is often done after disease is detected, to the vast genetic diversity of A. fumigatus isolates [24, 26], and to the limitations of the various molecular subtyping methods.

Anaissie and Costa [27] have brought to our attention another possible source of Aspergillus infection: hospital water [4–6]. Although Aspergillus species have been recovered from hospital and municipal water in several countries [5, 28, 29], there is currently no definitive proof that water is an important source of human infection. To date, the clearest published evidence in support this hypothesis is a single case report (in abstract form) of a patient who died of IA. An isolate of A. fumigatus recovered from this patient had a randomly amplified polymorphic DNA profile that was identical to those of isolates obtained from the patient’s hospital room water, but which differed from those of other environmental isolates obtained during the same period from other locations [6]. Although hospital water is a feasible environmental reservoir for Aspergillus infection and has a precedent in nosocomial legionellosis, we are still far from proving its role and importance in the transmission of IA. In addition to hospital-based investigations, it will clearly be essential to conduct larger and better-controlled studies, which would include molecular typing of Aspergillus isolates, to look for potential sources of waterborne infection in the home environment.

IS ASPERGILLOSIS A PREVENTABLE INFECTION?

With the continuing increase in the number of immunocompromised patients, the prevention of opportunistic fungal infections, such as IA, has become an issue of major importance in the management of all at-risk groups. Specific host and environmental risk factors still need to be studied in greater detail for each patient group, although the sporadic nature of Aspergillus infection in individual hospitals may make it difficult to evaluate these factors in a systematic manner. Multicenter studies may offer a solution to this problem. Even if the relative importance of specific environmental risk factors, such as contaminated water, can be clarified, problems regarding the development of effective prevention strategies will remain.

Environmental control measures, which are designed to protect high-risk patients from exposure to mold spores at home or in the hospital, are difficult to implement. Barrier protection methods have an important role in prevention of Aspergillus infection during periods of hospital building work [30]. Housing immunocompromised individuals in rooms supplied with HEPA-filtered air has also helped to prevent the acquisition of this infection within the hospital [11, 13, 31]; however, this approach is expensive, and, although it is feasible for the highest-risk groups for limited periods, air filtration has never been cost-effective for all groups at risk. It does not appear to be an option for patients who are being managed on an outpatient basis. If it is established that hospital water is a source for nosocomial aspergillosis, then disinfection of water supplies and measures to decrease patient exposure might be appropriate control strategies, as has been the case with legionellosis. Again, the feasibility and cost implications of these additional control measures would need to be examined.

Regardless of where most Aspergillus infections are acquired, novel approaches to prevention are needed. These may include the use of antifungal prophylaxis, although there is currently no convincing evidence that the available agents or regimens are effective in reducing the incidence of aspergillosis. Nevertheless, now that high-risk patients are spending more time outside of the hospital setting, the cost benefits of antifungal prophylaxis require careful evaluation. The high incidence of infection, coupled with a high mortality rate, supports the use of prophylaxis for IA in allogeneic hematopoietic stem cell transplant recipients as well as in liver and lung transplant recipients. In light of the much lower incidence of the disease in autologous hematopoietic stem cell transplant recipients and other solid-organ transplant recipients, routine antifungal prophylaxis may not be indicated. Other promising therapeutic approaches that deserve further evaluation include specific strategies designed to boost the immunological response of the host.

It would seem that, regardless of
whether the usual source of *Aspergillus* infection is contaminated air or water, prevention of this lethal disease will continue to be a challenge. As the number of susceptible hosts continues to increase, it seems likely that the incidence of IA will rise. Larger and better-designed epidemiologic studies of this disease will be crucial in the development of effective prevention strategies.

**References**