Editorial

Nosocomial Aspergillosis: How Much Protection for Which Patients?

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Aspergillus is unusual among nosocomial pathogens in several ways:

- The inanimate environment is the source of the organisms. The only other nosocomial pathogens for which the environment matters are *Legionella* and, perhaps, Clostridium difficile.
- Outbreaks of nosocomial aspergillosis may include patients infected by more than one spedies. This arises because the outbreaks result from breakdowns in ventilation permitting introduction of a variety of airborne opportunistic fungal spores.
- Virtually all nosocomial aspergillosis could be prevented if enough money were available. Unfortunately, this goal requires amounts of money that cannot be rationally allocated.
- Nosocomial aspergillosis cases are more highly concentrated in a specific population—immunosuppressed patients—than any other type of nosocomial infection.
- Prevention of nosocomial aspergillosis requires the participation of persons—architects, hospital designers, housekeepers, maintenance and engineers—who are not used to the needs involved.

The emphasis must be on prevention of nosocomial aspergillosis because the condition is so difficult to diagnose and treat. In the most highly immunosuppressed patients, when there is no pre-existing pulmonary disease, a positive coughed sputum culture in the presence of a pulmonary infiltrate has sufficient sensitivity and specificity to be useful in the clinical diagnosis of invasive pulmonary aspergillosis.[1] However, less highly immunosuppressed patients are much more likely to require bronchoscopy or transthoracic aspiration to recover the organism.

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Furthermore, many patients with chronic bronchitis have bronchial *Aspergillus* colonization sharply reducing the specificity of a positive culture from any pulmonary source. Such patients require biopsy to establish the presence of invasive aspergillosis. Detection of circulating antigen has been proposed as a diagnostic method[2] but awaits confirmation.

Treatment of nosocomial aspergillosis in highly immunosuppressed patients is ineffective. Bone marrow transplant recipients who have not engrafted, even while receiving empiric amphotericin therapy, can acquire aspergillosis, disseminate and die within a week or two. Less immunosuppressed patients, such as solid organ transplant recipients, can confine their pulmonary aspergillosis to fungus balls which can be successfully treated by amphotericin. However, if the aspergilli metastasize to the brain, the outcome is almost always fatal.

Klimowski, Rotstein and Cummings[3] perform several valuable services with their 20-year survey of nosocomial aspergillosis occurring in Roswell Park leukemia patients. They confirm with their larger data set earlier work[4] suggesting that nosocomial aspergillosis among leukemia patients is most common in those with acute or chronic myelogenous leukemia. Since the patient characteristic correlating most strongly with nosocomial aspergillosis is granulocytopenia,[4,5] itis reasonable to speculate that the predisposition to aspergillosis among acute myelogenous leukemia and chronic myelogenous leukemia patients results from the use of chemotherapies targeted to myelocytic elements.

They provide additional evidence that patients undergoing allogeneic bone marrow transplantation have the highest nosocomial aspergillosis rates of all.[5,6]

They provide the best long-term study establishing that nosocomial aspergillosis is on the rise. Introduction of cyclosporine may have mitigated the problem somewhat in solid organ transplant recipients[7] but the increasing use of bone marrow transplantation

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and the greater use of more aggressive chemotherapeutic regimens for a variety of malignancies have more than made up for it.

If clinical diagnostic criteria for aspergillosis are difficult to construct, criteria for surveillance purposes are even more elusive. We traditionally and rationally require a higher probability of infection to declare a clinical event aspergillosis in a research study than we would to decide to institute therapy. Furthermore, for surveillance purposes, consistency is more necessary. Klimowski et al.[3] require histological demonstration of tissue invasion. Although any consistently applied definition would allow them to make their fundamental conclusions, this definition results in an underestimate of the magnitude of the problem. Regardless of the definition chosen, uncultured or unbiopsied living patients and unautopsied dead patients result in missed cases. Since the fraction of patients undergoing autopsy is generally declining, we may not only be underestimating the aggregate problem, we may be underestimating the extent to which it is becoming more severe. Of course this problem of missed diagnoses may confound other conclusions. The apparent greater predisposition of bone marrow transplant patients may be magnified by a greater diagnostic avidity or a higher percent autopsied.

Assignment of an established case of invasive aspergillosis to a nosocomial or community-acquired etiology also presents problems. Since pulmonary colonization may occur in patients with underlying pulmonary disease, some cases classified as nosocomial may have resulted from aspergilli acquired prior to hospitalization. Most patients are not subjected to an extensive search for colonizing aspergilli at the time of hospitalization. Even if such surveillance cultures were negative it can always be asserted that pre-existing colonization is present at sufficiently low organism densities to escape detection.

Finally, patient peregrination produces a difficult confounder. Hospitalized patients may go on pass, tour the hospital grounds, visit courtyards or indoor spaces with less highly filtered air. Even patients who remain indoors may travel past construction or to older, less protected areas of the hospital for certain diagnostic studies or therapeutic procedures. Doubtlessly some infections are acquired in such circumstances and attributed to a nosocomial etiology even though there could be debate about the appropriateness of the attribution.

The available evidence suggests that prevention of nosocomial aspergillosis requires reduction in the spore content of the patient's ambient air.[8] This is accomplished by a combination of filtration of supply air, reduction of infiltrating and introduced spores and increases in air change rate.[9] Consideration of measures to accomplish these goals quickly becomes a matter of diminishing returns. Outside air has 1-10 *Aspergillus* **CFU/m^3.** The first 50% reduction in patient room ambient spore content can be accomplished by crude filtration and closed windows. Ambient spore concentrations of 0.1 *Aspergillus* CFU m^3 can be reached in modern hospitals with top-of-the-line bag filtration, standard air change rates and moderate efforts to prevent infiltration. However, further reductions in ambient spore content require substantial capital outlays, significant increases in operating expenses and intrusive and/or burdensome modifications of procedure.

Accomplishing ultra low ambient air spore content requires a book-length discussion. We have accomplished ambient spore contents in the range of 0.01/mm^3 in rooms with point-of-use HEPA filtration, air change rates of l0/hr, efforts to reduce infiltration from surrounding hospital areas or outside the building and upgraded corridor air filtration. But even at this level of spore contamination, *Aspergillus* cases continue to occur. Further reductions in spore content require laminar airflow rooms. These rooms have air change rates in excess of 100/hr.

How much reduction is enough? Which patients should be cared for in these expensive protective environments? Clearly allogeneic bone transplant recipients anchor the extreme end of the vulnerability spectrum. They require maximum efforts not only because of' their high incidence of aspergillosis, but because their period of vulnerability, at least in those who successfully engraft, is limited. If they can be brought through this period without an intervening, fatal infection, they have a very high probability of long life.

However, in some instances, the death of a patient due to nosocomial aspergillosis represents only a very marginal infection control failure. After standard preventive efforts, the survival of an adult with myelogenous leukemia is more highly, dependent on the severity of the disease than anything else. When aspergillosis brings such a patient to death after a third or fourth attempt at induction and several months of granulocytopenia, the probability that extensive efforts to provide nearly spore-free air would have saved such a patient is remote.

The hospital has an even lesser obligation to provide ultra low spore air for patients with a long-term duration of immunosuppression. For example, aspergillosis is an important problem for cardiac transplant recipients.[7] In the first several weeks after cardiac transplantation, the degree of immunosuppression is only slightly greater than that which the patient permanently incurs. Since such a patient will be breathing outdoor air within several weeks after transplantation, the rationale for expensive efforts to provide ultra low spore air is weak.

Apart from bone marrow transplant recipients, the spectrum of need for ultra low spore air is a continuum. When special efforts are restricted to only certain patient rooms, the issue of which patients have the greatest need for more highly protected rooms can become very contentious. Even for those placed in special rooms, protection while out of the rooms remains a problem. Ultimately, the best solution is to minimize ambient air spore content on a hospital-wide basis.

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