Leading article

The prevention of invasive aspergillosis—a realistic goal?


Amongst the different clinical syndromes caused by Aspergillus species which range from allergic bronchopulmonary aspergillosis to malignant otitis externa, invasive aspergillosis—an aggressive and potentially fatal infection—stands out as a major diagnostic and therapeutic challenge. Invasive fungal infections, such as aspergillosis, are significant causes of disease in the severely ill and immunocompromised, including those receiving solid organ transplants and in particular neutropenic cancer patients (Weber & Rutala, 1989). This is reflected by a burgeoning increase in use of antifungal agents such as amphotericin B: at Duke University Hospital, for instance, the number of vials of the latter drug dispensed in 1978 was 200 but this had risen to 5490 by 1988 (Perfect et al., 1991). Infections caused by fungi, in particular cryptococcosis, are also important causes of disease in AIDS patients. Invasive aspergillosis although uncommon in this group, is increasingly recognized. A recent paper reviewed 18 cases of aspergillus infection in AIDS patients, while antemortem colonization was recorded in a larger number (Pursell, Telzak & Armstrong, 1992). Other patients who may develop aspergillosis include solid organ transplant recipients, patients with multi-organ failure and children with inherited idiopathic immunodeficiency states. However, overall the incidence of invasive aspergillosis, even in those predisposed is variable and unpredictable.

Some hospital units diagnose this infection regularly in contrast to other units. Much of our knowledge concerning the epidemiology and control of aspergillosis has come from studies of the neutropenic patient, particularly those suffering from the leukaemias. In one recent survey of cancer centres in Europe, Japan and Canada reporting on systemic fungal disease at autopsy, aspergillosis was more common in some units while the frequency of candidosis was generally similar in all centres (Bodey et al., 1992). What factors account for the variable distribution of this potentially lethal infection?

One important explanation is the fact that Aspergillus species forms a major part of the airborne spore flora in many parts of the world at certain seasons (Mullins, Hutcheson & Slavin, 1984). Similarly, aspergillosis may follow exposure to environmental sources (Rhame et al., 1984). In some cases, notably the invasive paranasal forms of aspergillosis, the source of the infection is endogenous and focal colonization is followed by invasion. A recent study of surgical wound infections caused by Aspergillus spp. showed that the only significant risk factor was chronic respiratory disease (Richet et al., 1992); an explanation for this association is the higher rate of pulmonary Aspergillus spp. carriage in such patients. However, in most circumstances there is little evidence that long term carriage precedes infection. Indeed repeated reporting of outbreaks of invasive aspergillosis supports the view that peaks of exogenous exposure may account for the variable and unpredictable occurrence of infection, particularly in the neutropenic patient (Rogers, 1986), although variations in other factors, such as treatment regimens, cannot always be excluded. The sources of aspergillus spores include contaminated ventilatory and air conditioning systems, potted plants and, in particular, building work carried out in or near hospitals. The latter has been shown to generate high concentrations of airborne spores which are susceptible to simple measures of dust control, such as screening work areas, which thereby reduce the levels of contamination (Opal et al., 1986). The connection between building activity and aspergillosis is now well established, although we still do not adequately understand the precise conditions necessary for generating aerosols sufficient to cause disease, such as the types of construction/demolition work or environmental climatic factors. Despite this deficiency in our knowledge, control of aspergillosis by preventing exposure of patients to the organism or through pre-emptive drug therapy are logical approaches.

The main reason for continuing concern
about invasive aspergillosis is the well documented relationship between established infection and mortality in cancer patients. Mortality from invasive pulmonary aspergillosis (IPA), for instance, exceeds 90% when treatment is delayed 12 days beyond the first sign of infection (Aisner, Schimpff & Wiernik, 1979). While this earlier work does not take into account the wider use of preventative measures and protective isolation it does make the point that delay in the initiation of treatment is associated with high mortality in the leukaemic patient. However, the diagnosis of IPA is difficult because the earliest clinical signs are non-specific and the frequency with which organisms are isolated from sputum culture is very low. Serological cross-reactivity and low antibody titres to Aspergillus spp. in severely ill patients are major obstacles to accurate diagnosis. The detection of antigenic products of these organisms in serum, sputum or bronchial lavage fluid has also proved unrewarding apart from the detection of aspergillus galactomannan (Dupont et al., 1979). Even when antigen tests are positive the response is generally transient and of limited diagnostic value.

In the face of such continuing difficulties in confirming the diagnosis of invasive aspergillosis attention has turned to the use of preventative measures. The main approaches have involved protective isolation of patients at risk or the use of antifungal chemotherapy. Several studies suggest that the use of high efficiency particle air filtration (HEPA) or the provision of laminar air flow cubicles reduces the incidence of aspergillosis in neutropenic cancer patients (Rogers, 1986; Sherertz et al., 1987). While this approach has to be weighed against the disadvantages of isolation of the patient and cost (Armstrong, 1984), it limits exposure during hospitalization, apart from those occasions when patients move to different parts of hospital for investigative procedures.

Little work has been carried out on the use of preventative or pre-emptive antifungal chemotherapy in neutropenic patients at risk from aspergillosis. The early empirical use of intravenous amphotericin B has been used to reduce the incidence of fungal infections including those caused by Aspergillus spp. (Pizzo et al., 1982; EORTC International Antimicrobial Therapy Cooperative Group, 1989). Liposomal amphotericin B (AmBisome) has also been used in a similar manner with some success, although analysis of the data has proved difficult (Chopra et al., 1991). Other approaches, which accord more closely with the concept of chemoprophylaxis, have been the use of low dose continuous amphotericin B (Rousey et al., 1991), while intranasal amphotericin B which has been tried in a number of units with variable degrees of success (Meunier et al., 1987; Jeffery, 1991). Inhaled (nebulized) amphotericin B, has also been shown to reduce the rate of aspergillosis when compared with historical controls (Conneally et al., 1990). In this report of 34 patients during 144 episodes of neutropenia, there were no cases of aspergillosis in those receiving nebulized amphotericin B compared to an infection rate of 11.4% in historical controls from the same unit (Conneally et al., 1990).

The use of oral itraconazole represents another possible approach to the prevention of aspergillosis in the neutropenic patient. One study of the prophylactic use of this drug showed a significant reduction in the infection rate compared with historical controls who had received ketoconazole (Tricot et al., 1987). A further study of early itraconazole treatment for patients with Aspergillus spp. infections during a period of ward reconstruction also showed an encouraging response, except in those patients with continuing neutropenia (Brincker et al., 1991). However, the reduced absorption of the capsular form of itraconazole in bone marrow transplant recipients and AIDS patients means that reliable serum, and, presumably, tissue levels are difficult to obtain (Heykants et al., 1990) in a significant proportion of those most at risk. A new cyclodextrin formulation of itraconazole is better absorbed in these groups of patients and offers a potential solution to this problem (Smith, Barker & Hay, 1993).

The chief disadvantages of many of the studies to date has been the use of historical controls or recruitment of small numbers of patients with varying degrees of neutropenia, so that reliable interpretation of the data is not possible. However, now that a number of different approaches to the control of systemic fungal infections, including invasive aspergillosis exist, there is a need for large well designed comparative studies. A recent encouraging trend in the evolution of antifungal prophylaxis has been the establishment of a number of large multicentre studies designed to answer these questions.

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References


