Aspergillus: the invisible threat

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Invasive aspergillosis occurs in immunosuppressed patients. Chris Kibbler describes the cause of this fungal infection, and its diagnosis and medical management

KEY WORDS
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Although the media constantly regales the public with stories of 'killer' infections, few people are aware of their daily exposure to a fungus that can cause fatal infections in a susceptible host. It has been estimated that at least as many die from invasive aspergillosis each year as from meningococcal sepsis.

The reason why these deaths fail to make the headlines is probably because the individuals concerned were struck down without warning but already had an immunosuppressive disease. Many of these patients had undergone curative therapy for, or were in remission from, life-threatening conditions such as acute leukaemia or organ failure, only to die from invasive aspergillosis.

If this infection could be prevented and patient outcomes improved, health care professionals could have a significant impact on the overall outcome for patients, particularly those with haematological malignancy and those undergoing organ transplantation.

Where does *Aspergillus* species come from?

Aspergillus species are soil moulds, but are capable of living just about anywhere in the environment where there is a little moisture and basic substrate on which to base their saprophytic existence.

Outdoors they are associated with rotting vegetation, such as that present in compost heaps, damp grain and other agricultural settings. In buildings they are found in damp wallpaper and plaster, fireproofing, pipe lagging and air-conditioning systems (Manuel and Kibbler, 1998).

As a result, most of the air that we breathe contains conidia (spores) or hyphal fragments (filament-like structure) of the fungus, although the concentration varies considerably.

For example, one survey found that 74 per cent of homes in Scotland had significant levels of airborne *Aspergillus* species compared with 9–29 per cent of homes examined in a US study (Piecková and Jesenská, 1999).

The concentration also varies with the season – most Northern Hemisphere studies show higher levels in the autumn and winter months (Manuel and Kibbler, 1998).

Recently concerns have been raised over the presence of *Aspergillus* species in water (Anaissie et al, 2003).

Who does *Aspergillus* affect?

The fungus can cause four types of disease in humans:

- It may grow slowly, without invading tissue, in an abnormal site within the body, such as a pre-existing lung cavity (this is known as saprophytic disease);
- It may cause allergic disease (such as alveolitis or sinusitis) in those who have developed a hypersensitivity to the fungus;
- It may produce toxins (such as aflatoxins) in foodstuffs, which cause disease when ingested.
- Invasive aspergillosis, which is described in this article.

False colour scanning electron micrograph (SEM) of the spore-bearing bodies of the fungus Aspergillus fumigatus

Invasive aspergillosis

This almost always occurs in immunocompromised individuals. With the increasing number of such patients, invasive aspergillosis (IA) – along with other invasive mycoses (diseases caused by fungi) – had risen to seventh place in the list of infective causes of death by 2001 (McNeil et al, 2001).

In the USA, population-based studies have found an annual IA incidence of 12.4 per million (Rees et al, 1998). The UK incidence is less well understood and probably underestimated. Recent figures of 1.69 cases per million of the population for the year 1999 (Lamagni et al, 2001) were based on voluntary reporting.

The incidence varies according to the patients' underlying condition. For example, more than 20 per cent of heart-lung and lung transplant recipients and less than one per cent of patients with systemic lupus erythematosus became infected with IA (Denning, 1998).

One of the problems with assessing incidence is the fact that proof of diagnosis is difficult to obtain and many patients are treated on the basis of probable or

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possible infection. This issue will be discussed later in this article.

The mortality rate associated with IA is about 50 per cent and has changed little in the past decade. Some patient groups, such as bone marrow transplant recipients and people with Aids (both with 86 per cent mortality rates) are more likely to die, but most groups have mortalities in excess of 40 per cent (Lin et al, 2001).

Why does *Aspergillus* invade tissue? We all inhale particles of *Aspergillus* species, but in order to establish infection, the conidia need to germinate. This usually occurs in the alveoli of the lungs, although infection can occur anywhere in the respiratory tract, and, less commonly, elsewhere in the body.

The primary defence against germination is the alveolar macrophage. Any hyphae that do escape this and begin to invade tissue are usually eliminated by neutrophils. Consequently, immunosuppressive therapy (including high-dose corticosteroids) and neutropenia are the major risk factors for IA.

The clinical features and diagnosis of invasive aspergillosis Classical features of invasive pulmonary aspergillosis, responsible for about 90 per cent of primary disease, include cough, pleuritic chest pain, haemoptysis and shortness of breath. Involvement of the sinuses may be characterised by facial pain, epistaxis, nasal obstruction and orbital involvement.

However, in both cases, particularly in the neutropenic patient, initial symptoms may be little more than a fever.

In order to standardise diagnostic criteria, for the purposes of clinical studies and publication, the European Organisation for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) of the US National Institutes of Health published a set of diagnostic criteria for all invasive fungal infections in patients with haematological malignancy (Ascioglu et al, 2002).

These consist of combinations of host, clinical, mycological and tissue features, allowing a classification into possible, probable and proven infection.

One of the most helpful investigations is the high-resolution CT scan and this is included in the EORTC/MSG criteria. The 'halo' sign and subsequent cavitation are highly specific for IA. (The 'halo' sign is a mass or nodule, which is surrounded by a more radioluscent area). Some studies have shown them to be about 90 per cent specific in the neutropenic population.

Positive culture from a normally sterile site is relatively uncommon with IA. About 50 per cent of lung samples with histological evidence of IA yield positive cultures, so other means of identifying the causative fungus are needed.

A commercially produced ELISA (Enzyme-Linked Immunosorbent Assay), which is capable of detecting galactomannan (a constituent of the cell wall and one of the major circulating antigens of the fungus), has been shown to have high sensitivity and specificity in IA when used on serum or bronchoalveolar lavage samples.

Levels fluctuate, so it is necessary to measure them several times a week in serum in order to diagnose early disease. By doing so, one study found that IA could be detected a median of six days prior to clinical presentation (Maertens, 1999).

Polymerase chain reaction (PCR) has been found to be even more sensitive than the galactomannan ELISA, although a little less specific (Einsele, 1997). It needs to be used in the same way as the ELISA, although recently published research has found it to be useful in identifying *Aspergillus* species in a culture-negative tissue samples (Paterson et al, 2003). It also has the advantage of allowing other fungi to be identified.

It should be noted that a positive ELISA result is only sufficient to classify a case as probable by the EORTC/MSG criteria. PCR is not included at all, although this may change in the future, when the methodology becomes standardised and commercially available.

The prevention of invasive aspergillosis *Aspergillus* species are almost constantly present in the air and the major route of acquisition is by inhalation. Consequently, if the air can be rendered free of infective particles the disease should be preventable. This has been attempted using laminar airflow rooms with

TABLE 1. CURRENTLY LICENSED ANTIFUNGAL AGENTS THAT ARE EFFECTIVE IN THE TREATMENT OF INVASIVE ASPERGILLOSIS

CLASS	AGENT
Polyene	Amphotericin B lipid complex
	Liposomal amphotericin B
	Amphotericin B colloidal dispersion
	Conventional Amphotericin B
Triazole	Itraconazole
	Voriconazole
Echinocandin	Caspofungin

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positive-pressure air supplied through high-efficiency particulate air filters (HEPA) or using the same process without laminar flow.

This has been shown to reduce the risk to patients during the first 40 days following stem cell transplant by more than five-fold and is probably one of the reasons why most cases of IA in stem-cell transplant recipients now occur after the neutropenic phase (McWhinney et al, 1993; Wald et al, 1997).

Most of these are associated with graft-versus-host disease and graft failure, by which time the patient is no longer being nursed in a protective environment.

However, some patients still develop the disease in rooms supplied with filtered air. This is either due to failure of the system to exclude the fungus, previous exposure and colonisation prior to entering the room, or leaving the room during neutropenia for investigation or therapy. So additional means of prevention are clearly needed for high-risk patients.

Chemoprophylaxis There have been many studies of antifungal chemoprophylaxis in neutropenic patients and other at-risk groups. None have shown any significant benefit in preventing IA.

However, a recent meta-analysis has found that itraconazole, if given at a high enough dose, is protective and currently appears to be the most effective prophylactic agent for the disease.

Treatment of invasive aspergillosis

There are three classes of antifungal agents that are active against *Aspergillus* species:

- Polyenes;
- Triazoles;
- Echinocandins.

The agents that are currently licensed are shown in Table 1. Published data give efficacies of between 40–50 per cent for the different antifungals, although this includes partial as well as complete responses. The best results are obtained with early treatment and recovery of immune function, particularly neutrophil activity.

Amphotericin B For many years, amphotericin B was considered to be the best therapy for IA. It was appreciated that nephrotoxicity was likely in the 1mg per kg per day doses required, and that acute toxicity, in the form of rigors, fever and nausea, was very common. However, the drug was cheap and there were few alternatives.

Lipid formulations of amphotericin B, used in doses of 3–5mg per kg per day, have been shown to be at least as effective as the conventional preparation and have far less toxicity. Unfortunately, they are up to ten times as expensive.

Itraconazole This has good in-vitro activity against *Aspergillus* species and has been used in treatment for a number of years, particularly for more chronic forms of the disease and for oral continuation treatment after intravenous treatment has stopped. Unfortunately, it was not well absorbed in the neutropenic population and that limited its use until the intravenous formulation became available.

Voriconazole A recent randomised comparative controlled trial has found that the newly licensed voriconazole is significantly more effective than amphotericin B and is associated with a lower mortality (Herbrecht et al, 2002). Consequently, it is becoming increasingly difficult to justify the use of conventional amphotericin B for IA.

Caspofungin This is the first of the echinocandins to be licensed and it seems to have roughly equivalent activity with the other agents in the treatment of IA (Maertens, 2002). It has the benefit of low toxicity and, while more data and experience accrues, it is mostly being used at present as salvage therapy for those who develop toxicity to other agents or fail treatment with them.

Combined therapy In view of its mechanism of action, targeting the cell wall rather than the ergosterol in the cell membrane, there is much interest in combining caspofungin with other agents such as amphotericin B, or triazoles such as itraconazole or voriconazole. However, as yet there are no clinical data to support this.

Surgery

In some patients surgery is needed to manage massive haemoptysis or erosion of bony structures, and has been found to have an outcome at least as good as medical therapy alone, even when performed in neutropenic and thrombocytopenic patients (Yeghen et al, 2000).

Conclusion

With its rising incidence and high mortality, there is much to be done in the management of IA. It is to be hoped that refinement of the new diagnostic tests (and the way in which they are used) along with the advent of new antifungal agents will have an increasing impact over the next few years.

However, it is likely that mortality will remain high in certain risk groups and the search for better preventative strategies for these must continue. ■

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