Epidemiology

Michael Ellis, Malcolm Richardson, Ben de Pauw

Invasive fungal infections have emerged as important causes of hospital related morbidity and mortality. They are increasingly seen in patients not previously considered at risk, e.g. patients on an intensive care unit.* Candida albicans *and* Aspergillus *spp. are the most common pathogens, posing challenges in epidemiology, control and treatment.

Fungi rank seventh in the causes of infection-related deaths in the USA. Fungal pneumonia, urinary, surgical and bloodstream infections (BSIs) increased by 50%, 100%, 200% and 400% respectively from 1980 to 1990 (Jarvis, 1995). Fungaemic patients have a two-fold increased risk of dying compared to bacteraemic patients. Twenty-five per cent of patients with malignancy have invasive fungal infection (IFI) often only diagnosed at autopsy (Dean and Burchard, 1998).

AGENTS OF IFI

The majority of IFI involve *Candida* and *Aspergillus* spp. Few prospective studies, variable protocols and infection definitions limit accurate descriptions. Particular patient populations and geography determine organism distribution. A study which applied standardized laboratory-based case definitions to a defined USA population gave a broad view of mycotic infections (Rees et al, 1998). The cumulative incidence of IFI in the San Francisco bay area was 178.3/million population/year (*Candida* 72.8%, *Cryptococcus* 65.5%, *Coccidioides* 15.3%, *Aspergillus* 12.4%, *Histoplasma* 7.1%). Underlying conditions included human immunodeficiency virus infection (HIV; 47.4%), malignancy (21.7%), diabetes mellitus (9.9%), chronic liver disease (9.3%), abdominal/cardiac surgery (7.6%), haemodialysis (3.1%) and organ transplantation (1.3%). Recent sharp rises in candidiasis (27 times), particularly in the elderly, and aspergillosis (50 times) are noteworthy.

NOSOCOMIAL CANDIDAL INFECTIONS

These account for around 8% of nosocomial pathogens, 10% of hospital BSIs, and contributing 72% of nosocomial fungi mycoses. Seventy-six per cent of isolates are *C. albicans*. Major independent risk factors for systemic candidiasis are clear (*Table 1*) (Wright and Wenzel, 1997).

Patients with malignancy

This group is the most immunologically deprived, IFI vulnerable in which the risk factors for candidaemia include acute leukaemia, particularly acute lymphoblastic leukaemia (ALL), prolonged chemotherapy, mucosal colonization, central venous catheterization and neutropenia. In some centres candidal infections among leukaemic patients are falling, probably as a result of azole prophylaxis (Abi-Said et al, 1997) while invasive aspergillosis (IA) is increasing (Groll et al, 1996; Rees et al, 1998). In others and among solid tumour/lymphoma patients yeast BSI are increasing: in China there was a 27-fold increase in candidaemias over 13 years, especially *C. tropicalis* (Hung et al, 1996).

Candida non-albicans (CNA) species, particularly *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. lusitaniae,* account for up to 50% of candidaemias compared to 20% 15 years ago.

TABLE 1.
Independent risk factors for invasive candidiasis

Candida species colonization
Central venous catheters
Neutropenia
Haemodialysis
Chemotherapy
Multiple antibiotic use

Professor Michael Ellis is Professor of Medicine in the Faculty of Medicine and Health Sciencs, United Arab Emirates University, and Consultant in Infectious Diseases, Tawam Hospital, Al Ain, Abu Dhabi, United Arab Emirates, **Dr Malcolm Richardson** is Senior Lecturer in Clinical Mycology at the Haartman Institute, University of Helsinki, Helsinki, Finland, and **Professor Ben de Pauw** is Professor of Haematology, University Medical Center, Nijmegen, The Netherlands

Correspondence to: Professor M Ellis

This is more pronounced in haematology than solid tumour patients. These isolates are resistant to antifungal therapy. Mucosal colonization with CNA spp. significantly increases during fluconazole prophylaxis (Ellis et al, 1994). The EORTC and others suggested that fluconazole prophylaxis was independently significantly associated with the presence of CNA (Abi-Said et al, 1997; Viscoli et al, 1999). Variable study designs, institution bias and a concurrent increase in aggressive chemotherapies are potential confounders in assessing fluconazole's role. The inability of fluconazole to prevent and control some candidaemias is a worrying development.

Geographical institutional variability in candidaemia species distribution and antifungal susceptibility occurs. In some hospitals the incidence among haematological patients is very low, e.g. <1% in the Karolinska Institute, compared to 30% in many USA hospitals. In North America 43.8% of candidaemias were caused by CNA, compared to 59.5% in South America (Pfaller et al, 1998a,b). Resistance to fluconazole or itraconazole was 20% in regions of north-west and south-east USA but only 5.5% in the north-east and south-west (Pfaller et al, 1998a,b). DNA fingerprinting probes have provided evidence that local influences determine microevolutionary outcomes.

HIV patients

Disseminated candidiasis has only recently been recognized in patients with advanced HIV disease, the incidence rising over 10-fold over the last decade or so. Risk factors include prolonged central venous catheterization, multiple parenteral antibiotics, CD4 counts <100, bacterial sepsis and malnutrition. *C. albicans* accounts for two-thirds of cases, with *C. glabrata* and *C. krusei* in others receiving fluconazole. Mortality is 38%, predicted by CNA strains and neutropenia (Tumbarello et al, 1999).

Intensive care patients

One half of nosocomial candidaemias occur in intensive care units (ICU) (Pfaller et al, 1998a,b) — around 7 per 10 000 patient days. ICU stay is an independent mortality risk factor in candidaemic patients. The overall mortality is 60%, and the attributable death 20%. IFI occur commonly in ICU patients with severe underlying illness, multiple courses of antibiotics and intravenous catheters (Flanagan and Barnes, 1998). Risk factors for death include multiorgan dysfunction, haemodialysis, delay in instituting antifungal therapy and APACHE score >21. Specific risk groups within ICU display more tailored risk factor profiles, e.g. in critically ill trauma patients only hyperalimentation predicts IFI compared to steroids, central venous catheters or antibiotics in the general ICU population — it is more likely that these represent markers of injury severity (Borzotta and Beardsley, 1999). However, IFI diagnosis in an ICU setting is difficult because of the non-specific signs and superficial fungal colonization (Flanagan and Barnes, 1998).

Burns patients

Of burns patients, 4% have candidaemia, and the risk increases with the number of body sites colonized. The loss of skin barrier and intestinal mucosal atrophy switches *Candida* from a colonizer to invader. Ileus necessitates central venous parenteral nutrition which predisposes to invasive candidiasis. Antibiotics disturb the normal balanced microbial flora in favour of yeasts, and CD4, immunoglobulin or phagocyte dysfunction lowers defences.

Paediatrics

Candidaemia accounts for 21% of paediatric nosocomial BSI. *C. parapsilosis* is the causative agent in 24–49% of cases (Stamos and Rowley, 1995). Mortality is lower than that for adults (attributable mortality 15–20%) is caused by the predominance of this organism, which is less adhesive and adherent to mucosa, less virulent and invasive. Prematurity and cardiac disease occur in 80%. Femoral or central venous catheters, topical antifungals, candiduria and prolonged hyperalimentation are significantly associated with candidaemia but hyperalimentation independently predicted candidaemia. Antibiotic therapy and endotracheal intubation/tracheostomies are important associations. The better survival in children could be related to high frequency of early infected catheter removal and tolerability of intravenous conventional amphotericin B.

Surgical patients

Gastrointestinal surgery risks peritonitis, intra-abdominal abscess, ventilatory dependence, multiple organ failure and surgical wound fungal colonization. APACHE scores >10, ventilation for more than 48 hours or use of multiple antibiotics predict IFI (Dean and Burchard, 1998). Significant candiduria (>10^5 colonies/ml), multiple site colonization or candidal peritonitis increase candidaemia risk, as shown by the subsequent reduction in disseminated candidiasis using pre-emptive antifungal drugs.

Central venous catheters, total parenteral nutrition

Breach of skin epithelial integrity permits skin candidal organisms, particularly *C. parapsilosis,* to colonize the plastic intrusive devices, seeding candidaemia. The catheter itself may be a target for candidaemia or a surrogate marker for candidaemia caused by total parenteral nutrition. Total parenteral nutrition causes glutamine-mediated mucosal atrophy, immunological depression (complement fixation, immunoglobulin deficiency, macrophage dysfunction) and supports fungal growth (*C. parapsilosis*).

Antibiotics

Antibacterial antibiotics create an ecological niche by reducing the normal bacterial flora. Loss of bacterial-mediated inhibition of candidal mucosal cell adhesion and higher sustained intestinal *Candida* concentrations (Dean and Burchard, 1998) facilitated by vancomycin and imipenem generate high stool concentrations of *Candida* spp. and nosocomial candidaemia (Jarvis, 1995).

SOURCE OF INFECTION

C. albicans and many other species present in food are introduced into the gut which they colonize. *C. tropicalis* and *C. parapsilosis* are found in soil and plants. Candidaemia could arise from the patient's flora through translocation, as local/systemic immunity becomes impaired (endogenous source). Molecular techniques confirm this by showing identity of colonizing and infecting strains. The stringent infection control measures practised on leukaemia or bone marrow transplant units have been associated with only rare instances of environmentally-acquired candidal infections.

Recent studies indicate *C. albicans* acquired directly or indirectly from contaminated environmental sources and spread to patients via the hand of health-care workers (exogenous source) (Fidel et al, 1999). Therefore de novo *C. glabrata* infection in bone marrow transplant patients is related to prolonged hospitalization and environmental contamination. *C. glabrata* and *C. parapsilosis* can be introduced from patients into the hospital environment which functions as a reservoir for onward transmission to other patients.

INVASIVE ASPERGILLOSIS

The 130 *Aspergillus* spp., which are ubiquitous in the soil, atmosphere, snow, deserts and plants, are found in hospital ventilation systems, mattresses and patients' rooms. *A. fumigatus* is the commonest species causing IFI in humans, followed by *A. terreus*, *A. flavus*, *A. nidulans*, *A. oryzae* and *A. niger*. The interest in this pathogen relates to the wide spectrum of disease from simple respiratory tract colonization, bronchitis, lung cavitary colonization, allergic bronchopulmonary aspergillosis to fulminant invasive disease in the extreme immunocompromised.

IA typically occurs in the setting of severe and protracted neutropenia, and is found particularly in patients with haematological malignancy or bone marrow transplants. There are other well-defined risk groups (*Table 2*). There is increased reporting of patients outwith the regular risk groups, e.g. HIV patients or rheumatology patients. Recent studies indicate that IA causes 20–40% of IFIs in cancer patients — a substantial rise over the last 20 years (*Figure 1*) (Groll et al, 1996). Such figures are a result of the increasing immunosuppressive intensity such patients are currently experiencing and possibly a greater awareness of the diagnosis. Among bone marrow transplant patients IA accounts for 70% of all non-candidal IFI. The outcome from IA is considerably worse than that from invasive

TABLE 2.
Important risk factors for invasive aspergillosis

Severe (<100 x 10^9/ml) and prolonged (> 10 days) neutropenia
Neutrophil dysfunction
High dose steroid therapy
Graft *vs* host disease following bone marrow transplantation
Solid organ transplantation acute rejection
Cytomegalovirus disease post transplantation

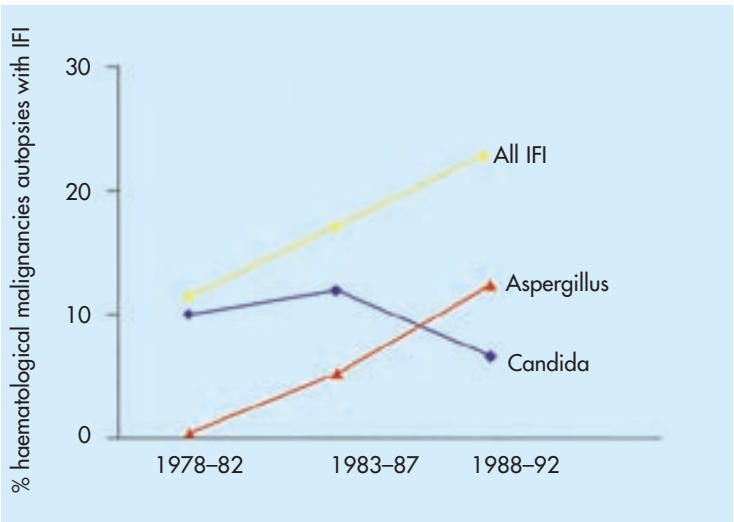

Figure 1. Invasive fungal infections (IFI): autopsy evidence. From Groll et al (1996).

candidiasis. This may be a result of the greater difficulty in making an early precise diagnosis, the rapidity with which *Aspergillus* grows (*Figure 2*) and its life-threatening angio-invasive and haemorrhagic potential. Outcome is related not only to target organ but to underlying disease (*Figure 3*).

The absence of precise mycological diagnostic information impedes representative epidemiological studies. In a recent updated multicentre prospective study among haematology patients IA was diagnosed definitively in only 50% of the 123 patients included (Denning et al, 1998). Lung (87%) and sinus (16%) were the commonest target sites, and 64% died. Patient groups at risk were those with acute myeloid leukaemia (49%), ALL (17%), lymphoma (9%) or bone marrow transplant patients (12%).

The source of *Aspergillus* is generally assumed to be the hospital environment. Air sampling studies indicate that hospital walls, ceilings and ventilation systems are colonized with *Aspergillus* and other moulds. These strains remain for months or years (Leenders et al, 1999). The portal of entry is the nasopharynx, and after colonization that focus provides a source for sinus, pulmonary and haematogenous disease. A major association with outbreaks of IA in hospitalized patients is the sudden rise and dispersal of viable spores caused by building. This is paralleled by air concentrations rising above 1 cfu/m^3 (cfu = colony forming unit) and the number of clinical cases fall as counts fall below 0.01 cfu/m^3. Not all studies have confirmed this correlation. High efficiency particulate air (HEPA) filtration and laminar air flow dedicated rooms produce a virtually *Aspergillus* condia-free environment. This is associated with a significant decrease in IA cases, and is good evidence for the relevance of an environmental source (Cornet et al, 1999).

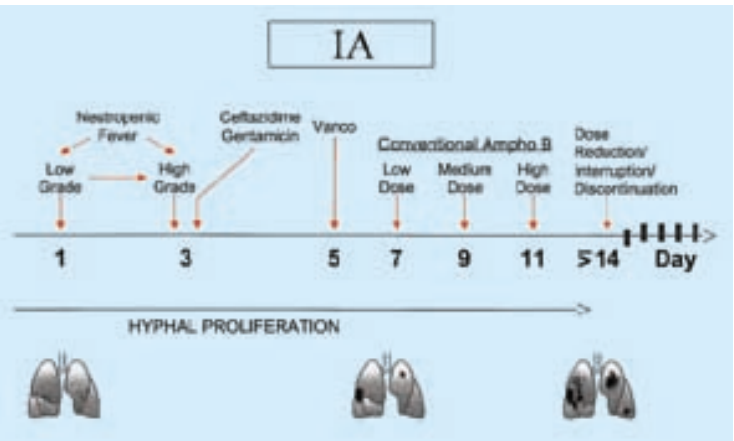

Figure 2. Invasive aspergillosis (IA): rapid fungal growth and therapeutic delay.

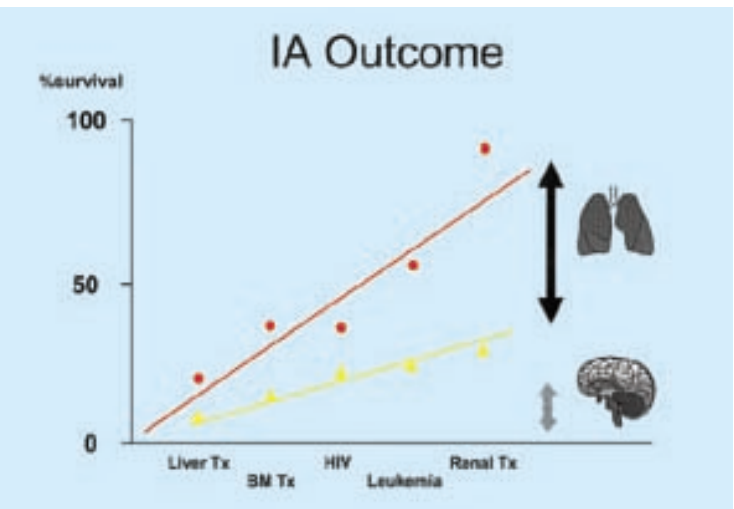

Figure 3. Invasive aspergillosis (IA): outcome relation to target organ and underlying disease. BM = bone marrow; Tx = transplant.

The use of molecular epidemiological tools have in some instances confirmed traditional thinking that IA cases arising in the same clinical unit have a common source, by demonstrating that the isolates are genotypically identical. This is strengthened by concurrently using different tests, e.g. random amplification of polymorphic DNA technique, multi-locus enzyme electrophoresis and sequence-specific DNA probes.

However, these techniques have not always confirmed identity between immediate environmental and disease strains. For example, IA in bone marrow transplant patients can be caused by strains different from those found in the hospital environment. This might be explained by sampling error, or the infection could have been acquired from outside of the hospital or from a source not generally accepted as harbouring the fungus, e.g. water supplies. This latter suggestion has been supported recently and could explain cases arising in HEPA-filtered environments (VandenBergh et al, 1999). Patients can also reactivate a previous IA focus.

Enormous genotypic diversity exists among strains, even in clusters of cases. However, since patients probably inhale the same diverse spore population it does not follow that the different genotypes found in patients have not been acquired from the same hospital environment. It has been hypothesized that 8000 different genotypes could be inhaled by a hospitalized patient in a 3-month period (Chazalet et al, 1998). Clearly the current enthusiasm for molecular epidemiological studies is an exciting area with the potential to clar-

ify many issues. The genetic variability of *Aspergillus* has also suggested the existence of a hitherto unidentified sexual or parasexual reproductive stage.

EMERGING FUNGAL PATHOGENS

In 1963 five *Candida* species were known to cause human disease; there are now more than 20. These include *Malassezia* spp., *Rhodoturula* spp., *Hansenula* spp., *Trichosporon* spp., *Blastoschizomyces* spp. and *Prototheca* spp..

Fusarium spp. closely follows *Aspergillus* spp. as the most common filamentous fungal pathogen in some hospitals. Moulds with melanin-like pigments in their cell walls (dematiaceous) include *Cladophialophora bantiana*, *Bipolaris* spp., *Dactytaria* spp., *Pseuallerscheria boydii* and *Scedosporium prolificans* — associated mortality is >60%.

Penicillium spp. in general are innocuous. There are reports of these organisms causing life-threatening disease and not always in the immunocompromised. Disseminated *P. marneffei* infection is the third commonest AIDS-defining illness in Thailand. Ubiquitous in soil, the bamboo rat is implicated in spread to humans. The pulmonary alveolar macrophage is the principal receptor — commonly dysimmunoregulated in HIV infection. The disease is often mistaken for tuberculosis, histoplasmosis or cryptococcosis. HM

Conflict of interest: none.

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KEY POINTS

- Invasive fungal infections are now significant contributors to infection-related deaths.
- Nosocomial candidiasis is the commonest invasive fungal infection and occurs not only in patients with malignancy, but those with human immunodeficiency virus (HIV) infection, burns, intravascular catheters, and those who have undergone surgery, are staying on an intensive care unit or who have taken antibiotics for prolonged periods.
- Prolonged hospitalization, environmental contamination, person to person spread are all incriminated in establishing patient reservoirs of *Candida*.
- Invasive aspergillosis accounts for 70% of all non-candidal invasive fungal infections, is underdiagnosed, and is being seen increasingly in non-classical risk groups such as patients with HIV and rheumatoid disease.
- Aspergillosis is generally thought to occur following inhalation acquisition of spores from hospital surfaces (and possibly through water supplies); however, molecular epidemiologics suggest other as yet unclear routes.
- Emerging invasive fungal pathogens include *Malassezia, Trichosporon, Fusarium, Scedosporium* and *Penicillium* spp.