Epidemiology of invasive fungal infections due to *Aspergillus* spp. and Zygomycetes

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**ABSTRACT**

An increased incidence of invasive fungal infections, especially those caused by filamentous fungi, has been observed among high-risk patients such as allogeneic stem-cell transplant recipients and those with acute leukaemia receiving high-dose chemotherapy. Despite significant progress in the prevention and treatment of fungal infections, invasive aspergillosis continues to be a major cause of morbidity and mortality. Development of more efficient therapeutic and prophylactic strategies with currently available and new antifungal agents, as well as of sensitive and specific methods for early diagnosis, is needed. In addition, an increasing incidence of invasive infections caused by Zygomycetes is of concern. Several reports of breakthrough zygomycosis in patients receiving voriconazole have raised the possibility of a relationship between voriconazole use and increased risk of Zygomycetes infection, although evidence of a definite causal relationship remains controversial. The potential impact that all therapeutic and prophylactic changes can have on the emergence of ‘new’ pathogens should be kept in mind.

**Keywords** Invasive fungal infections, *Aspergillus*, zygomycetes

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**INTRODUCTION**

An increased incidence of invasive fungal infections has been particularly evident in patients with cancer over the past decades, particularly in haematopoietic stem-cell transplant recipients and patients with haematological malignancies [1–7]. In addition, a marked shift in the spectrum of causative organisms is increasingly being reported, with filamentous fungi gaining predominance. Indeed, until the 1990s, candidiasis was the most common invasive fungal infection in neutropenic patients, whereas during the past decade, invasive mould infections have become the most frequent fungal infections among patients at high risk, especially those receiving allogeneic stem-cell transplants or very intensive chemotherapy for acute leukaemias [8,9]. Although several explanations can be given for this radical change in the prevalence of fungi in invasive mycoses, the routine use of fluconazole prophylaxis, the increased intensity of chemotherapy, and the growing practice of allogeneic stem-cell transplantation from unrelated donors over the past decade, among other factors, clearly seem to be involved. In addition, although *Aspergillus* spp. account for the majority of invasive filamentous fungal infections, other emerging opportunistic fungal pathogens have been reported over the last 20 years [10–12]. The present review summarises some of the new developments in the epidemiology of invasive aspergillosis and zygomycosis.

**EPIDEMIOLOGY OF ASPERGILLOSIS**

Currently, invasive aspergillosis is probably the major clinical problem among invasive fungal infections. Although underlying conditions predisposing to this infectious complication include malignancy, haematopoietic stem-cell or solid-organ transplantation, and congenital or acquired immunodeficiencies, the present review focuses...
on epidemiological considerations in patients with haematological malignancies and in haematopoietic stem-cell transplant recipients, in whom invasive aspergillosis is the most prevalent mould infection and a major cause of morbidity and mortality.

During the last decade, several epidemiological factors have contributed to the increasing concern about invasive aspergillosis. Several reports have shown a rising prevalence of invasive aspergillosis upon autopsy over recent decades worldwide [13–17], surpassing invasive candidiasis as the most frequent fungal infection found at autopsy at some tertiary-care centres [1,15–17]. Moreover, this epidemiological increase in the incidence of aspergillosis and the decrease in candidiasis have been widely reported, not only at autopsy, but also upon evaluation of microbiological isolates from patients with a diagnosis of possible, probable or proven invasive fungal infection. The routine prophylactic use of fluconazole over the past decade is certainly implicated in the dramatic decrease in the incidence of invasive candidiasis, and has also contributed substantially to the emergence of invasive aspergillosis as the most common invasive fungal infection [16].

We have observed similar epidemiological changes in our Leukaemia and Stem Cell Transplant Unit at the University Hospital La Fe. We identified 131 cases of invasive aspergillosis between January 1988 and December 2003 (Fig. 1). During the first half of this period, the incidence of invasive aspergillosis was relatively stable at 25 cases per 1000 admissions, while in the last 8 years it has continuously increased. Acute leukaemia and allogeneic haematopoetic stem-cell transplantation are also the most frequent underlying conditions in our Haematology Unit. Although several factors may have been involved in the increase in the incidence, it should be noted that the number of allogeneic stem-cell transplants, especially those using bone marrow and cord blood from unrelated donors as the source of stem cells, has significantly increased at our institution during recent years. Among 407 stem-cell transplants performed from 1999 to 2003, the overall incidence of invasive aspergillosis was 6.8%, but it has dramatically increased from less than 2 per 100 transplants during the first 3 years to 17.5 per 100 transplants during the last year (Fig. 2). We can speculate about a possible nosocomial cluster associated with hospital construction works, defects in air-handling equipment, and other environmental factors; however, the number of cases may sometimes appear to be a cluster when in fact it is not [17]. Although it is still too early to evaluate the individual impact of several measures that were implemented almost simultaneously to decrease the incidence of aspergillosis in our unit, it seems that the introduction of systematic itraconazole prophylaxis for patients with acute leukaemia and for allogeneic stem-cell transplant recipients has certainly contributed to the attainment of a significant reduction (unpublished data).

Although the incidence of invasive aspergillosis in other haematological malignancies, e.g., multiple myeloma, non-Hodgkin’s lymphoma, and other lymphoproliferative diseases, is much
less than that reported in patients with acute leukaemia, an increase in opportunistic infections has been also suggested, including invasive fungal infections, in parallel with the use of more aggressive therapeutic approaches during recent years. The use of more intensive chemotherapy and highly immunosuppressive drugs, e.g., fludarabine or alemtuzumab, has certainly contributed to an improved outcome of lymphoproliferative diseases, but it has also increased the risk of opportunistic infections, including invasive aspergillosis.

It is generally accepted that the epidemiology of invasive aspergillosis is complex and that many epidemiological issues still remain controversial. Regarding the nosocomial or community-acquired origin of this particular fungal infection, it is assumed that most cases of invasive aspergillosis in immunocompromised hosts are of nosocomial origin, the air being the most important source of *Aspergillus*. However, the proportion of patients who become infected from alternative sources has not been well-determined. In fact, a considerable number of cases of invasive aspergillosis in allogeneic stem-cell transplant recipients occur in the outpatient setting. In these patients, who are severely immunosuppressed for prolonged periods after engraftment, with alternating periods of hospitalisation and home residence, but always under potent immunosuppressive therapies, it is very difficult to establish the actual origin of the infection in individual cases.

To add to the complexity of and the concern about the potential sources of *Aspergillus* contamination, a recent study found that cotton fabric harbours and disperses *Aspergillus* spores more readily than other types of fabric [18]. This finding leads us to speculate that cotton clothing worn by hospital personnel and visitors may serve as a source of *Aspergillus* exposure for susceptible patients [1]. Finally, as Kontoyiannis and Bodey reported recently [1], the available epidemiological evidence implicating the hospital water reservoir systems in the acquisition of nosocomial invasive aspergillosis is weak [19] and still remains controversial [20].

Despite the significant progress in the treatment of invasive aspergillosis, the mortality rate is still high and the financial burden of invasive aspergillosis-associated hospitalisation is enormous.

Epidemiology of Zygomycosis

Within the class Zygomycetes, the order Mucorales includes the genera *Rhizopus, Mucor* and *Rhizomucor*, which are the pathogens most frequently implicated in human zygomycosis. Several recent reports have called attention to the increase in the incidence of invasive infections caused by the Zygomycetes, particularly in recipients of haematopoietic stem-cell transplants and patients with haematological malignancies. However, contrasting with infection by other filamentous fungi that mainly target immunocompromised hosts, zygomycosis is frequently observed in a broader population of patients, including those with poorly controlled diabetes mellitus, and those receiving deferoxamine therapy for iron overload, among others [2]. As with aspergillosis, the present review focuses on epidemiological considerations in patients with haematological malignancies and in haematopoietic stem-cell transplant recipients.

The epidemiology and outcome of this emerging life-threatening fungal infection have been outstandingly reviewed recently by Roden *et al.* [2]. This is the first comprehensive review in the English-language literature concerning zygomycosis since the original case report in 1885. This review analyses 929 eligible cases in whom the zygomycosis had been confirmed either histologically or by culture, and describes the underlying condition, the anatomical location of infection, the surgical and antifungal treatments, and the outcome. Although the first reported case of zygomycosis was in 1885 [21], the first eligible case that met the predefined criteria was reported in 1940.

One of the most striking observations during the course of writing this review was that diabetes was the most common underlying condition (36%), and the next largest patient population had no primary underlying disease (19%). Furthermore, malignancy was an underlying condition in the third largest patient population (17%), with haematological malignancy being the underlying condition in 95% of these cases. Regarding the sites and patterns of infection, there were significant differences according to the host population. The patterns observed in patients with malignancy and in stem-cell transplant recipients are shown in Table 1. The lungs constituted more than one-half of all sites of infection in patients...
with malignancy and in stem-cell transplant recipients (60% and 52%, respectively), while sinuses were the second most common site involved in these patients.

_Rhizopus_ and _Mucor_ were the most commonly recovered genera (50% and 18%, respectively). In this study, zygomycosis was apparently more prevalent among males. Finally, multivariate regression analysis of risk-factors showed that disseminated disease, renal failure and infection with _Cunninghamella_ species had an adverse influence on mortality. Pulmonary, rhino-cerebral, kidney and gastrointestinal infection were associated with the highest risk of mortality.

Recently, attention has been called to the possible association of voriconazole with an increased risk of infection caused by Zygomycetes [12]. This association is supported by several reports of breakthrough zygomycosis in patients receiving voriconazole [22–26]. Voriconazole has broad-spectrum antifungal activity and is especially active against _Aspergillus_ species and other filamentous fungi, but it has no activity against the Zygomycetes [27]. However, a definite causal relationship between treatment with voriconazole and the emergence of breakthrough infections caused by Zygomycetes is far from established. In fact, although the use of voriconazole may have contributed to the occurrence of zygomycosis, there are some data indicating that the incidence of zygomycosis was increasing before the introduction of voriconazole into clinical practice [12]. Data from two large transplant centres in the USA show that an increase in the incidence of zygomycosis was already apparent in the mid-1990s [28,29], leading to speculation that the apparent increase in the incidence of zygomycosis may be an amplification of this phenomenon [12]. However, a recent prospective surveillance study of 27

### Table 1. Patterns of zygomycosis in different haematological conditions (data from Roden et al. [2])

<table>
<thead>
<tr>
<th>Type of infection by site</th>
<th>Malignancy (%)</th>
<th>Stem cell transplantation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Rhino-cerebral</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Sino-orbital</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

patients with zygomycosis (case-control observational study) carried out at the MD Anderson Cancer Center found that voriconazole prophylaxis was a factor that favoured zygomycosis [30].

### CONCLUSIONS

In the context of an increasing incidence of invasive fungal infections in patients with haematological malignancies and in haematopoietic stem-cell transplant recipients, filamentous fungi have increasingly been reported as the causative organisms over the past decade. Despite significant progress in the prevention and treatment of fungal infections, invasive aspergillosis is still a major cause of morbidity and mortality in these patients. More efficient therapeutic and prophylactic strategies, involving the currently available antifungal agents and new antifungal agents, as well as sensitive and specific methods for early diagnosis, are needed. The potential impact that therapeutic and prophylactic changes can have on the emergence of ‘new’ pathogens should be kept in mind. For example, the possible association of the use of voriconazole and an increased risk of infection caused by resistant organisms such as Zygomycetes has been reported recently.

### REFERENCES


