

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

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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

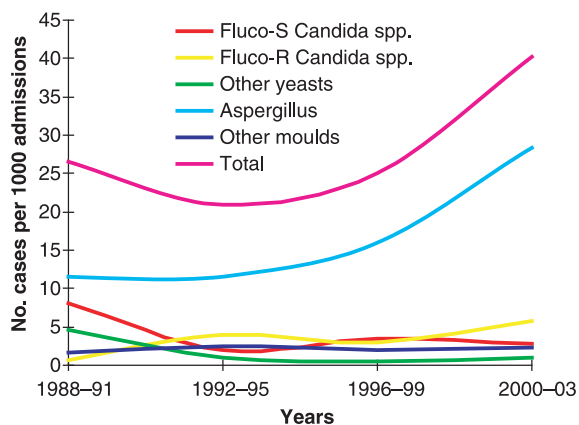


Fig. 1. Trends in fungal infections (probable and proven cases) in the Haematology Service at University Hospital La Fe over a 15-year period. Fluco-S: Fluconazole-susceptible; Fluco-R: Fluconazole-resistant.

stable at 25 cases per 1000 admissions, while in the last 8 years it has continuously increased. Acute leukaemia and allogeneic haematopoietic 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

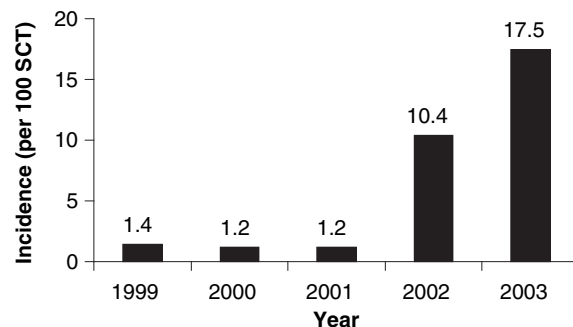


Fig. 2. Incidence of aspergillosis in stem-cell transplant (SCT) recipients in the Haematology Service at University Hospital La Fe (1999–2003).

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