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Review

Reviewing the importance and evolution of fungal infections and potential antifungal resistance in haematological patients

Alessandro Busca [a,*], Anna Maria Tortorano [b], Livio Pagano [c]

[a] Stem Cell Transplant Center, Department of Oncology and Hematology, AOU Città della Salute e della Scienza, Corso Bramante 88, 10126 Turin, Italy
[b] Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy
[c] Catholic University of the Sacred Heart, Rome, Italy

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ABSTRACT

There is a growing body of evidence supporting the emergence of azole resistance in *Aspergillus* and *Candida* spp. and this may be of particular concern due to the potential implications in the management of invasive fungal infections occurring in immunocompromised hosts. The aim of present review was to describe the magnitude of the problem, summarising the epidemiology and potential impact of yeast and mould antifungal resistance in patients with haematological malignancies. The first cases of triazole-resistant *Aspergillus fumigatus* isolates were reported in 1997 in patients receiving itraconazole. More recently, a worrisome increase in the frequency of azole resistance has been reported, primarily in patients with chronic forms of pulmonary aspergillosis. However, estimates of azole resistance in haematological patients are poorly characterised, although widespread use of antifungal prophylaxis might favour the emergence of resistant isolates in this setting. A French study estimated a prevalence of 0.85% azole resistance among 118 *A. fumigatus* isolates collected in 89 haematological patients. More recently, the epidemiology of azole resistance in *A. fumigatus* in a cohort of 762 haematological patients who received an allogeneic haematopoietic stem cell transplantation (HSCT) in two German centres has been reported. *A. fumigatus* was identified in 27 HSCT recipients, and 8 patients (30%) had azole-resistant invasive aspergillosis. In summary, the rate of azole-resistant isolates in patients with haematological malignancies appears to be low; however, the paucity of data currently available requires further prospective surveillance programmes.

Contents

1. Introduction

Invasive fungal infections (IFIs) represent one of the most relevant life-threatening infectious complications occurring in patients with haematological malignancies [1–3]. During recent years, several reports have indicated an overall increase in the incidence of IFIs among haematological patients [4,5]. The apparent increase in the incidence of invasive aspergillosis (IA), as reported by several studies, may be explained at least in part by the fact that diagnoses only suspected in the past are now more easily established due to the wide application of serum biomarkers

* Corresponding author. Tel.: +39 011 633 5359; fax: +39 011 633 5759.
E-mail address: abusca@cittadellasalute.to.it (A. Busca).

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[i.e. galactomannan and (1,3)-β-D-glucan] and early use of chest computed tomography (CT) scanning. On the other hand, recent data suggest that the mortality rate of IA has decreased. The SEIFEM Group compared the attributable mortality rate due to IA in 2002 and 2006 in patients with acute leukaemia recruited in six Italian haematological centres. Despite an overall increase in the incidence of IA (6% in 2002 vs. 13% in 2006), there was a trend towards a reduction in the attributable mortality rate (24% vs. 13%) [6]. Similarly, other studies have shown decreased mortality due to IFIs [7–9].

In this respect, the availability of different antifungal agents may be considered an essential weapon for the treatment of IFIs.

The first antifungal agent developed for the treatment of IFIs was nystatin; however, the presence of severe toxicity hampered its use as a systemic agent.

When introduced in 1959, amphotericin B deoxycholate (AmBD) was a life-saving drug, and clinical experience over 50 years has proven that this compound is effective although toxic.

For many years conventional amphotericin B (AmB) has been considered the gold standard for first-line therapy of patients with IFI. Given their superior safety profile, lipid formulations of AmB have now replaced AmBD in many circumstances, although these new drugs have not been evaluated in comparative trials as first-line therapy but rather tested and licensed for salvage therapy in patients with progressive fungal infection or in patients in whom AmBD was not tolerated.

Similarly, the echinocandins have been investigated as initial therapy for IA in several clinical trials including haematological patients and stem cell transplant recipients, although the results were moderately disappointing, leading to a lower grade of recommendation in the majority of published guidelines [10,11]. Azoles represent the backbone of therapy for treating immunocompromised patients with IFI. In 2002, Herbrecht et al. reported the results of a prospective randomised study comparing voriconazole (VCZ) and AmBD for the treatment of IA in the immunocompromised hosts, showing that VCZ was able to achieve better responses and improved survival, resulting in fewer severe side effects than the standard approach with AmBD [12]. The results of this study led to the inclusion of VCZ in the majority of international guidelines with a high strength of recommendation and quality of evidence [13]. In addition, two large studies have supported the use of VCZ as prophylaxis of fungal infections in patients receiving allogeneic haematopoietic stem cell transplantation (HSCT) [14,15].

2. Trends in epidemiology

Antifungal prophylaxis has greatly changed the epidemiology of fungal infections in patients with haematological malignancies. In the 1980s, the most frequently diagnosed fungal infection was candidiasis. Widespread use of fluconazole (FLZ) prophylaxis decreased the incidence of invasive *Candida* infections in this patient population [16,17]. However, this decline was associated with an increased percentage of bloodstream infections caused by non-*albicans Candida* spp. Whilst *Candida albicans* predominates as cause of bloodstream infection in all patient groups, this yeast accounts for only 35–36% of cases occurring in patients with haematological malignancies. *Candida tropicalis* and species characterised by primary or secondary resistance to FLZ, such as *Candida glabrata*, *Candida krusei*, *Candida norvegensis* and *Candida inconspicua*, are frequently isolated [18–21].

Among HSCT recipients enrolled in the Transplant-Associated Infection Surveillance Network, the most frequent species causing invasive candidiasis were *C. glabrata* ($n = 92$ cases; 33%), followed by *C. albicans* ($n = 55$; 20%), *Candida parapsilosis* ($n = 39$; 14%), *C. tropicalis* ($n = 23$; 8%) and *C. krusei* ($n = 17$; 6%) [22].

Since the early 1990s, IA has become the predominant invasive fungal disease in patients with haematological malignancies as well as in HSCT recipients [23–25]. In more recent years, with the availability of compounds with good to excellent activity against *Aspergillus* spp., infections caused by difficult-to-treat opportunistic fungi such as Mucorales, *Fusarium*, *Scedosporium*/*Pseudallescheria* and *Trichosporon* have been increasingly reported [24–26].

The emergence of these organisms is multifactorial and can be related to more intense immunosuppression, prolonged survival of severely immunosuppressed patients, and selective pressure of broad-spectrum antifungal agents used for prophylaxis or therapy.

The widespread use of VCZ has been recognised as a possible cause of the increased incidence of mucormycosis [27], which represents the second/third most frequently encountered mould infection in most haematology and HSCT centres, although it should be underscored that two large studies on antifungal prophylaxis did not show any potential increase of mucormycosis associated with the use of VCZ [14,15]. FLZ, echinocandins and flucytosine, but also VCZ, lack in vitro activity against Mucorales. In general, the most active drugs against these fungi are AmB and posaconazole (PCZ), which show differing activity depending on the genus and species of the infecting strain [28]. Isavuconazole has shown in vitro activity against Mucorales [29], and an open-label trial evaluating primary as well salvage therapy of mucormycosis showed similar efficacy of isavuconazole and either AmB or PCZ [30].

The range of organisms causing fungal infections in patients receiving antifungal prophylaxis continues to expand, and when fungal elements are seen in the blood the possibility of breakthrough infections caused by moulds known to grow in blood cultures, such as *Fusarium* and *Scedosporium*/*Pseudallescheria* spp., should be considered.

Scedosporiosis, albeit rarely encountered, is of particular concern as several species are characterised by innate resistance to many antifungal agents. *Scedosporium prolificans* is resistant to all licensed antifungal drugs, whilst VCZ and PCZ show good activity against *Scedosporium apiospermum*, *Pseudallescheria boydii* and *Scedosporium aurantiacum*.

Disseminated infections due to *Fusarium* spp. in patients with persistent neutropenia respond poorly to antifungal treatments, with death rates of up to 75%, and some species show significant levels of resistance to the common systemic antifungal agents. The results of susceptibility testing reveal a wide range of susceptibility, with *Fusarium solani* apparently resistant to most antifungals [31]. Data mainly based on experimental studies indicate a better prognosis for infections caused by *Fusarium verticillioides* than for those caused by *F. solani* owing to lower virulence and higher antifungal susceptibility [32].

Similarly, *Aspergillus* spp. less susceptible to antifungals have started to occur in the setting of patients with haematological malignancies and in HSCT recipients [33,34]. *Aspergillus terreus*, which accounts for up to 33% of cases in Austria, is often, although not always, reported as poorly susceptible to AmB [33,35,36]. *A. terreus* infection, which is rapidly progressive with dissemination observed in >60% of cases, is considered as a marker for patients at higher risk of treatment failure or death from underlying disease [33]. In a retrospective cohort study of 83 cases of invasive *A. terreus* infection, treatment with VCZ led to an improved outcome compared with the use of other antifungal therapies [33].

However, a recent multivariate analysis founds that *A. terreus* is associated with poor prognosis irrespective of the use of anti-*Aspergillus* azoles, thereby suggesting species-specific virulence factors as well as an increase in azole resistance [37].

Resistance to azoles and/or AmB is also reported in *Aspergillus ustus* and in rarely encountered cryptic species such as *Aspergillus*