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Potential role of aerosolized amphotericin B formulations in the prevention and adjunctive treatment of invasive fungal infections

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Abstract

The incidence of invasive fungal infections (IFIs) continues to increase, largely due to the steady rise in the number of at-risk patients and the increased use of aggressive immunosuppressant agents. Many available treatments are often limited by concerns about efficacy, safety, drug interactions, and/or cost. Owing to the poor treatment outcomes of immunosuppressed patients with IFIs, new preventative and treatment strategies are being investigated. Among these are the aerosolized formulations of amphotericin B. Published experience with the use of aerosolized amphotericin B deoxycholate (AmBd) in the prevention of IFIs has raised concerns regarding challenges in drug administration and tolerability. However, evolving data regarding administration of lipid-based formulations of amphotericin B indicate potential advantages over AmBd in the prevention and adjunctive treatment of IFIs.

Keywords: Amphotericin B; Aerosol; Invasive fungal infections; Prophylaxis

1. Introduction

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality, particularly in immunocompromised patient populations (most notably solid organ transplant (SOT) recipients, haematogenous stem cell transplant (HSCT) recipients, select surgical intensive care unit (ICU) patients, and those with prolonged neutropenia secondary to chemotherapy for malignancy) [1,2]. Risk factors identified in these patients include, but are not limited to, receipt of immunosuppressive therapy, prolonged neutropenia, environmental exposure, prior fungal colonization, broad-spectrum antibacterials, cytomegalovirus (CMV) coinfection, and graft-versus-host disease [1–4].

The incidence of IFIs is influenced by numerous factors, including the underlying patient population, period of observation, method of IFI detection, type and degree of immunosuppression, and environmental exposure (Table 1). However, *Candida* spp. are responsible for the vast majority of IFIs, most notably nosocomial bloodstream infections [1,6,7]. Patients undergoing HSCT or SOT are also at increased risk of infections due to *Aspergillus* spp. The incidence of invasive aspergillosis, however, differs significantly according to the type of transplantation involved (Table 2). Among patients undergoing HSCT, allogeneic recipients of unmatched donors experience the highest risk of invasive aspergillosis [5,9]. Recent data obtained from 4,621 HSCT patients at 19 US centers reported rates of 0.5%, 2.3%, and 3.9% in autologous, allogeneic matched and allogeneic unmatched patients at 12 months post-transplant, respectively [8]. Among SOT recipients, patients undergoing lung transplantation exhibit the highest incidence of invasive aspergillosis [5,10]. The incidence of aspergillosis in this patient population has been reported to range between 2.4% and 13% [8,11]. Finally, emerging fungal infections (such as *Fusarium*, *Zygomycetes*, and other moulds) have also been reported in selected patient populations, primarily those with prolonged and severe immunosuppression [1,12,13].

Historically, treatment outcomes for invasive infections in the immuncompromised patient population have been poor. For example, attributable mortality due to invasive candidiasis was reported to be 49% in one study [14]. For invasive aspergillosis, crude mortality exceeds 80% in pop-

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Table 1
Incidence of invasive fungal infections (IFIs) among solid organ transplant recipients

Transplanted organ	Incidence of IFI (%)	Proportion of *Aspergillus* infections (%)	Proportion of *Candida* infections (%)
Kidney	1.4–14	0–10	90–95
Heart	5–21	77–91	8–23
Liver	7–42	9–34	35–91
Lung/heart and lung	15–35	25–50	43–72
Small bowel	40–59	0–3.6	80–100
Pancreas	18–38	0–3	97–100

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ulations such as HSCT recipients and those with advanced HIV infection [2]. Mortality at 3 months post-transplant in HSCT recipients with aspergillosis was reported to be 84.6% [8]. Consequently, there is a need for new clinical strategies.

Administration of antifungal prophylaxis has been advocated in selected patient populations at high risk of infection. These include select HSCT and SOT recipients [3,15,16]. However, the optimal agent for prevention of IFIs is not known. In addition to targeted prophylaxis, the timely institution of appropriate antifungal therapy has often been hampered by the lack of sensitive and specific clinical, laboratory, and radiographic criteria for IFIs [17]. Therefore, development of methods to detect IFIs early in their clinical course may aid in improving treatment outcomes. Examples of such tests include the detection of galactomannan [18], 1-3 beta-D-glucan [19,20], and polymerase-chain-reaction assays [21]. Early detection may allow the institution of antifungal therapy prior to the onset of early disease symptoms (e.g. colonization, antigenemia) and prior to the emergence of serious illness. This is most commonly known as 'pre-emptive' therapy. The use of combination antifungal therapy, while controversial, is also gaining interest [22]. Finally, the role of 'traditional' antifungals administered in 'non-traditional' or novel methods has been reviewed as prevention and adjunctive therapy in severe or refractory cases [23]. An example of such administration includes the use of aerosol formulations of amphotericin B.

The objective of this review is to summarize the data regarding the use of aerosolized formulations of amphotericin B as prevention and adjunctive therapy for IFIs in the immunocompromised host.

Table 2
Invasive aspergillosis in haematogenous stem cell and solid organ transplant recipients

Transplant type	Incidence at 12 months post-transplant
Autologous HSCT ($N = 2588$)	0.5
Allogeneic HSCT ($N = 2033$)	2.9
Lung transplant ($N = 290$)	3.5
Liver transplant ($N = 1058$)	0.3
Heart transplant ($N = 349$)	0.8
Kidney transplant ($N = 2147$)	0.1
Other SOT ($N = 266$)	0.4

HSCT, haematogenous stem cell transplant; SOT, solid organ transplant. Reprinted with permission [8]. © 2005 Taylor & Francis.

2. Antifungal prophylaxis: in search of the ideal agent

A comprehensive discussion of antifungal prophylaxis is beyond the scope of this review. However, to put the potential role of aerosolized amphotericin B as a prophylactic strategy into perspective, issues surrounding the selection and administration of prophylactic treatment are briefly summarized.

Following identification of patients at highest risk of IFIs, the selection and administration of antifungal agents as prophylaxis require considerations of the agent's safety, efficacy, and cost. More specifically, the ideal prophylactic agent would possess the following characteristics: (1) efficacy established by randomized, controlled clinical trials; (2) acceptable safety profile; (3) sufficiently broad-spectrum antifungal activity to prevent the most prevalent aetiologies of IFIs; (4) easy to administer (e.g. oral rather than intravenous) and (5) free of significant drug interactions.

2.1. Evidence-based efficacy data

Administration of amphotericin B (both amphotericin B deoxycholate [AmBd] and lipid-based formulations of amphotericin B) have been investigated as a strategy for the prevention of IFIs in selected patient populations. For example, AmBd has been evaluated in HSCT recipients and compared with both placebo [24] and fluconazole [25]. Lower doses of AmBd (i.e. 0.1–0.2 mg/kg/day), relative to doses used for treatment of invasive IFIs, were employed. Generally, these studies demonstrated the potential of AmBd to reduce documented fungal infections, although tolerability was reduced when compared with fluconazole. Prophylactic administration of liposomal amphotericin B (L-AmB) [26–28] and amphotericin B lipid complex (ABLC) [28,29] have also been investigated as prophylaxis. However, administration of amphotericin B formulations in this population may be problematic due to issues of tolerability, cost, and the need for intravenous therapy [30].

Azole antifungals have been investigated extensively for the prevention of IFIs in selected populations. Results of these studies are reviewed in detail elsewhere [3,31–33]. The majority of these studies establish the role of fluconazole in reducing the incidence of invasive candidiasis in HSCT recipients [34,35], liver transplant recipients [36,37], and high-risk surgical ICU patients [38–41]. Itraconazole has been com-