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Aerosolized Delivery of Antifungal Agents

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Abstract Pulmonary infections caused by *Aspergillus* species are associated with significant morbidity and mortality in immunocompromised patients. Although the *treatment* of pulmonary fungal infections requires the use of systemic agents, aerosolized delivery is an attractive option in *prevention* because the drug can concentrate locally at the site of infection with minimal systemic exposure. Current clinical evidence for the use of aerosolized delivery in preventing fungal infections is limited to amphotericin B products, although itraconazole, voriconazole, and caspofungin are under investigation. Based on conflicting results from clinical trials that evaluated various amphotericin B formulations, the routine use of aerosolized delivery cannot be recommended. Further research with well-designed clinical trials is necessary to elucidate the therapeutic role and risks associated with aerosolized delivery of antifungal agents. This article provides an overview of aerosolized delivery systems, the intrapulmonary pharmacokinetic properties of aerosolized antifungal agents, and key findings from clinical studies.

Keywords Aerosolized antifungal · Antifungal · Drug safety · Nebulized antifungal · Amphotericin B · Caspofungin · Itraconazole · Voriconazole

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Introduction

Pulmonary infections caused by *Aspergillus* species are associated with significant morbidity and mortality in immunocompromised patients [1•]. Poor lung function coupled with immune suppression resulting from bone marrow or solid-organ transplantation can predispose patients to infections caused by *Aspergillus* [2]. In fact, approximately 20% to 25% of bone marrow or lung transplant recipients develop invasive pulmonary aspergillosis [2, 3].

Treatment of pulmonary fungal infections requires the use of systemic agents because there is a lack of data on aerosolized administration. However, aerosolized delivery of antifungal agents has been evaluated for *prevention* of invasive pulmonary aspergillosis. Aerosolized delivery is an attractive option, as high local drug concentrations are achieved with minimal systemic exposure, which is especially crucial owing to the adverse effects associated with systemic administration of some antifungal agents. Although aerosolization has been proposed for decades, data on the pulmonary pharmacokinetics, safety, and efficacy of antimicrobial agents administered by this method remain insufficient. Furthermore, drug products that are formulated exclusively for the purpose of aerosolization are limited.

Aerosolized Delivery Systems

An effective antimicrobial regimen optimizes the eradication of pathogenic organisms by achieving drug concentrations sufficient to yield maximum effect at the site of infection. Aerosolized administration delivers drug directly to the respiratory system to allow concentration of the antimicrobial agents at the site of infection and, equally

important, reduces systemic exposure. As a result, aerosolized administration of anti-infective agents maximizes efficacy and limits toxicities associated with the specific agents, making it an appealing option [4–7].

Drug administration by aerosol requires nebulization, which is the primary mode for pulmonary delivery of antimicrobial agents. Many different configurations exist for nebulization; the three main types are jet systems, ultrasonic systems, and systems that use a vibrating mesh/aperture plate [8•]. The type of nebulizer system can influence drug deposition into the airways, but optimal drug deposition, particularly deep in the respiratory tract, requires proper administration technique regardless of the system used [9]. Recommendations are available for aerosolized drug delivery in spontaneously breathing and mechanically ventilated patients [10, 11].

The physical properties of antimicrobial formulations (eg, size, viscosity, surface tension, osmolality, tonicity, and pH) will affect the degree of pulmonary penetration. One of the most important factors determining deposition into the small airways and alveoli is the particle size or mean mass aerodynamic diameter (MMAD). The MMAD of a particle is the diameter of the sphere with unit density that settles at the same rate as the particle. The optimal particle size for aerosol drug delivery is 1 to 5 micrometers (μm). Particles that are 1 μm or less are likely to be eliminated during exhalation, whereas particles that are 5 μm or greater are deposited into the oropharynx and swallowed [12]. Akin to particle size, viscosity also contributes to the efficiency of drug delivery. In fact, viscosity is inversely proportional to the rate of aerosolization. Viscosity greater than 1.5 centipoises dramatically decreases the rate of aerosolization [13].

Whereas some characteristics of aerosolized particles determine the depth of deposition and rate of aerosolization, other characteristics determine the observed toxicities, such as cough, which is a common adverse effect of aerosolized delivery. Physical properties of antimicrobial formulations, including osmolality, tonicity, pH, and surface tension, can greatly influence the occurrence of cough. Induction of cough can occur when the osmolality is less than 100 mOsm/kg or when it exceeds 1,100 mOsm/kg. Because aerosolized solutions are generally produced from intravenous formulations that contain preservatives (eg, phenols and bisulfites), these solutions are often hypertonic, with unadjusted pH values. These preservatives may contribute to cough, airway irritation, and bronchoconstriction. Surface tension of drug particles also may contribute to cough.

Jet Nebulizers

Although three main nebulizer systems are available, the most commonly used system for aerosolization of antifungal agents is the jet nebulizer. Two types of jet nebulizer systems are currently used in clinical practice: standard and breath-enhanced. The breath-enhanced nebulizer system demonstrates better drug delivery than the standard system, as 10% to 20% of the patient's inspiration must pass the nebulization chamber for aerosol generation; it is also associated with fewer quality control problems [14]. The optimal particle size for medications delivered via jet nebulizer systems ranges between 1 and 5 μm, allowing for drug deposition into the smaller airways (usually 1–2 μm or smaller for parenchymal deposition) [15]. A drug solution volume of 4 to 6 mL and flow rate of 8 L/min is recommended for jet nebulizers [16]. Some drug loss may occur, as residual ("dead") volumes of 1 to 3 mL fail to be nebulized.

To optimize delivery of the jet nebulizer system and minimize the residual volume, a cone-shaped nebulizer should be used. Improving the wetness of plastic surfaces and reducing the internal surface area of the nebulizer will also improve delivery. In contrast, humidity increases aerosol loss and may consequently decrease drug delivery by 40% [13, 17]. More drug delivery occurs late in the nebulization process because of evaporative loss of water from the drug solution. Advances in jet nebulizer systems are on the horizon, with attempts to decrease the loss of drug during exhalation and to limit environmental release of drug aerosols by using filters or one-way valves [15].

The main advantages of jet nebulizers are that they are inexpensive, disposable, and do not require special equipment. Microbial growth in improperly cleaned nebulizers is eliminated with disposable nebulizers. Some disadvantages are that power sources, equipment setup, and some cleaning for equipment maintenance are required. Notably, there are significant variations in performance of various nebulizers within the same brand and across different brands [16]. Therefore, they should not be used interchangeably when precise dosing is required for therapeutic response.

Aerosolized Antifungal Agents

Amphotericin B Products

Amphotericin B has broad activity against various yeasts, molds, and dimorphic fungi, including *Aspergillus* species. Its poor systemic distribution to the lungs results in the need for higher doses, which may place patients at increased risk for adverse drug reactions [18–20]. Furthermore, because amphotericin B exhibits concentration-dependent pharmacodynamics, optimal fungicidal activity relies on attainment of high drug concentrations—that is, a high ratio of maximum concentration (Cmax) to the minimum inhibitory concentration (MIC) [21]. Poor drug solubility following parenteral administration hampers this fungicidal activity of amphotericin B. Therefore, an

aerosolized formulation of amphotericin B may allow a lower dose to be used while maintaining high lung concentrations in patients with pulmonary fungal infections.

The unique particle structure and size of each amphotericin B product is inversely related to the aerosolized particle size. To achieve aerosolization, the large molecules of the various intravenous amphotericin B formulations—deoxycholate (AmBd), liposomal (L-AmB), colloid dispersion (ABCD), and lipid complex (ABLC)—result in small aerosolized particle sizes with MMAD ranging from 0.90 to 2.43 μm [22]. The variable sizes of these different aerosolized amphotericin B formulations influence the extent of alveolar distribution and half-life of the drug in the lungs [22–25].

The intrapulmonary pharmacokinetic properties of aerosolized amphotericin B have been evaluated using different doses and formulations of amphotericin B, as well as different types of nebulizers [3, 23, 26]. One study that evaluated the distribution of nebulized AmBd (6 mg) in 17 lung transplant recipients demonstrated preferential deposition in the allografted lung and a greater accumulation in the distal zones of the bronchial tree [3]. In addition, the use of RespirGard II (Marquest; Englewood, CO) and PariBoy or Pari IS II (both Pari Werke; Starnberg, Germany) for nebulization of AmBd has been shown to generate particles that deposit in the alveoli, trachea, and nasopharynx [27]. Based on a pharmacokinetic study in sheep, the maximum intrapulmonary concentration was not influenced by the dose (5 mg vs 30 mg) [28]. However, the area under the concentration-time curve was greater for the larger dose.

Another pulmonary distribution study evaluated 35 mg ABLC over 30 min using a breath-actuated jet nebulizer (N= 12) [26]. In contrast to AmBd, there was no significant difference in the amount of ABLC deposited between native and allografted lungs (3.9 mg vs 2.1 mg, P=0.2) in recipients of single lung transplants. However, a slightly larger dose was delivered to the right lung versus the left lung (4.0 mg vs 2.8 mg, P=0.06) in recipients of double lung transplants.

Nebulized L-AmB has been shown to exhibit biexponential kinetics with an elimination half-life of 22 days for neutral liposomes in an animal model [29]. This half-life offers an advantage over aerosolized AmBd, which has a half-life of 4.8 days [30]. In addition, the long half-life for L-AmB has been correlated with prolonged antifungal activity lasting up to 6 weeks [22]. A more recent study on tolerability in humans suggested that administration of L-AmB as infrequently as every 2 weeks may be adequate to prevent aspergillosis [31]. If true, this regimen may significantly improve patient compliance.

Investigational Agents

Several antifungal products specifically formulated for aerosolization are in various stages of development. An amphotericin B formulation containing liposomes coated with macrophage-specific ligands (O-palmitoyl mannan or O-palmitoyl pullulan) was created to augment selective presentation to alveolar macrophages [32]. Although studied only in a rat model, this formulation demonstrated higher localization and retention in lungs than aerosolized plain AmBd solution (three times more after 6 h). However, there was considerable systemic absorption (20% to 50%) with this new formulation.

Itraconazole has also been studied for aerosolization. Using a new nanotechnology technique that spray-freezes a drug with poor water solubility into a liquid, the effectiveness of aerosolized itraconazole as a prophylactic agent against invasive pulmonary aspergillosis caused by *Aspergillus flavus* and *Aspergillus fumigatus* has been studied in immunocompromised mice [33, 34]. Single and multiple aerosolized dose studies in mice have demonstrated the ability to achieve therapeutic pulmonary concentrations within 60 min after completion of nebulization while maintaining serum levels 25 to 50 times lower [35, 36]. Although results appear promising in mice, further studies are needed before extrapolating them to the clinical setting.

Despite its good distribution into the lungs, the intravenous formulation of voriconazole has been studied for aerosolization at quite low doses [37]. Therapeutic drug levels in human lung tissue occurred 30 min after inhalation of a 10 mg/mL solution [38]. Maximal pulmonary concentrations were 1.4 times higher than plasma concentrations, perhaps on account of the low potential for pulmonary metabolism and the high distribution across lung mucosal surfaces.

Pneumocandin, an older derivative of caspofungin, has been shown to be effective in delaying mortality for prophylaxis against invasive pulmonary aspergillosis in rats [39]. Aerosolization of caspofungin is currently being evaluated using three different jet nebulizer and compressor systems. The ability to achieve favorable physiochemical properties for nebulization requires dilution in normal saline and a more concentrated (30 mg/mL) solution. Further in vivo studies are needed to elucidate the role of aerosolized caspofungin [40].

Human Studies: Prophylaxis

Clinical experience with aerosolized antifungal agents is limited to various formulations of amphotericin B products, although itraconazole and caspofungin are currently under investigation. Amphotericin B has been the most studied aerosolized antifungal agent for prophylaxis against invasive aspergillosis in patients with hematologic malignancies and lung transplantation. Its use as an alternative agent for the treatment of invasive aspergillosis has been limited to

case reports rather than clinical studies [41, 42]. Therefore, only clinical studies for prophylaxis against invasive aspergillosis are reviewed in this section.

Hematologic Malignancies

Two groups of investigators performed dose-finding studies for aerosolized AmBd in neutropenic patients with hematologic malignancies. One observational study in stem cell transplant recipients (n=18) and leukemia patients (n=8) demonstrated that invasive aspergillosis was not observed with 5 to 20 mg of AmBd nebulized twice daily [5]. Prophylactic treatment was continued for the duration of neutropenia or until intravenous antifungal therapy was initiated. Notably, 14 (54%) of the patients required a switch to intravenous AmBd for fevers. None of the patients developed clinically suspicious or pathologically documented invasive aspergillosis. No adverse effects were reported with the use of nebulized AmBd.

Another dose-finding study in granulocytopenic patients with hematologic malignancies (N=42) showed the effectiveness of AmBd (5–10 mg) nebulized three times daily in preventing invasive fungal infections [43]. Though 88% of patients tolerated the regimen of 5 mg three times daily, only 48% tolerated a dose escalation up to 10 mg three times per day. Common adverse effects reported were mild cough and dyspnea, which occurred in 19% of patients. Invasive fungal infections developed in 28% of patients; there was no difference between any of the dosing regimens in the occurrence of fungal infections.

The largest randomized, unblinded, placebo-controlled, multicenter trial evaluated the effectiveness of inhaled AmBd in neutropenic patients (N=382) with hematologic malignancies, including leukemias, non-Hodgkin's lymphoma, or solid tumors requiring high-dose chemotherapy with autologous bone marrow transplantation [6]. The preliminary results of this study were published previously [44]. Patients were randomized to receive nebulized AmBd or no prophylaxis (including inhalational, oral, and parenteral routes) until resolution of neutropenia (median 27 days; range 2–50). Notably, no significant differences were detected in the development of invasive aspergillosis (4% vs 7%, P=0.37) and infection-related mortality (8% vs 7%, P=0.79) between those who received nebulized AmBd and placebo. Cough, bad taste, and nausea were the most commonly reported adverse effects in patients who received inhalation prophylaxis.

Safety and efficacy data with lipid formulations of amphotericin B in neutropenic patients with hematologic malignancies are more promising. In a prospective, open-label, noncomparative study, the safety and tolerability of aerosolized ABLC was evaluated in 40 recipients of allogeneic hematopoietic stem cell transplants [45]. Subjects received fluconazole concurrently with aerosolized ABLC treatment once daily for 4 days, then once weekly for 13 weeks. Overall, aerosolized ABLC was well tolerated, with reports of cough, nausea, taste disturbance, or vomiting in 2% of 458 total treatments. Although 5% of treatments resulted in reduced pulmonary function measurements, no patients required bronchodilators or withdrawal from the study. Although no participants developed invasive aspergillosis, three developed other invasive fungal infections, which were caused by *Fusarium* species, Zygomycetes, and *Candida glabrata*.

A recent randomized, placebo-controlled trial of L-AmB (12.5 mg nebulized twice weekly on consecutive days) was conducted in 271 patients with hematologic diseases who had expected neutropenia for at least 10 days; 139 patients received L-AmB and 132 received placebo [46••]. This study demonstrated a significant reduction in the incidence of invasive pulmonary aspergillosis with the aerosolized antifungal L-AmB (OR, 0.26; 95% CI, 0.09–0.72; P=0.05 using intent-to-treat analysis). However, cough occurred in 16 patients in the treatment group versus only 1 in the placebo group (P=0.002). Although no serious drug-related adverse events were reported, more patients in the treatment group discontinued therapy (45% vs 30% in the placebo group; P=0.01) because of weakness, technical problems with aerosolized delivery, and cough. Increase in serum creatinine was not observed in the treated patients.

Lung Transplantation

Amphotericin B via nebulization has also been evaluated in patients who received immunosuppressive medications following solid-organ transplantation (primarily lung transplants). One prospective, nonrandomized, uncontrolled study evaluated the effectiveness of prophylactic use of AmBd in 55 lung transplant recipients [47]. Patients received AmBd (30 mg nebulized three times daily) for 120 days after transplantation, then 30 mg daily for life. Using a multivariate analysis, the risk of developing aspergillosis was decreased with nebulized AmBd (OR, 0.13; 95% CI, 0.02–0.69; P<0.05). A few patients experienced mild adverse effects, but only one patient withdrew from the study, because of bronchospasm.

In a retrospective review of lung transplant recipients, oral voriconazole (n=65) was compared with oral fluconazole with or without inhaled AmBd (n=30) [48]. Itraconazole was substituted for fluconazole in patients colonized with *Aspergillus* (n=15). The rate of proven or probable invasive aspergillosis was significantly less in the voriconazole group than in the fluconazole/itraconazole group (2% vs 23%, P=0.001). Although the authors did not report the outcomes for patients who received inhaled AmBd, it was evident that voriconazole was superior despite the

presence of *Aspergillus* colonization in patients who received itraconazole with or without inhaled AmBd. Results from this review suggest that further data are needed to support the use of aerosolized antifungals in this population in light of the advent of mold-active azole antifungals, which are more easily administered than traditional agents.

In addition to AmBd, ABLC also has been evaluated in three clinical studies, one of which was a trial comparing AmBd and ABLC. In a prospective, noncomparative study designed to evaluate safety, aerosolized ABLC was subjectively well tolerated in 98% of 51 recipients of lung or heart-lung transplants [49]. No significant drug-related adverse events were reported. In another study, which retrospectively evaluated the effectiveness of ABLC nebulization, invasive fungal infections occurred in 2% of 60 lung transplant recipients [50]. Patients received ABLC (50 mg nebulized once every 2 days for 2 weeks) with oral fluconazole (200 mg every 12 h). Nausea and vomiting were reported in four patients.

A randomized, double-blind study compared two different formulations of aerosolized amphotericin B for the prevention of fungal infections in recipients of lung and heart-lung transplants [4]. In addition to bronchodilator treatment, patients received nebulized AmBd (25 mg daily) (n=49) or ABLC (50 mg daily) (n=51) for 4 days, then weekly for 7 weeks following transplantation. The doses were doubled for patients on mechanical ventilation. No significant difference in the development of invasive fungal infection was detected between the study groups within 2 months after treatment initiation (14% infection with AmBd vs 12% with ABLC). Notably, experiences of adverse events were more likely to occur with AmBd (OR, 2.16; 95% CI, 1.10–4.24; P=0.02).

Summary: Should Nebulized Amphotericin B Be Used for Prophylaxis?

Some evidence exists for prophylactic use of aerosolized amphotericin B formulations, including AmBd (20–25 mg once daily), ABLC (50 mg once daily), and L-AmB (12.5 mg twice weekly on 2 consecutive days), against invasive aspergillosis in non-mechanically ventilated patients with hematologic malignancies or lung transplantation. For patients on mechanical ventilation, the doses of AmBd and ABLC should be doubled. The lipid-based formulations, including L-AmB, appear to have favorable safety and pharmacokinetic profiles. Overall, few well-designed, randomized, controlled trials have assessed their efficacy. Based on clinical studies, which produced conflicting results, and consistent with a recommendation from the Infectious Diseases Society of America, routine use of nebulized amphotericin B cannot be recommended [1•]. More clinical evidence is necessary, particularly regarding the prevention of aspergillosis in lung transplant recipients.

Safety of Aerosolized Antifungals

One major advantage of aerosolized administration of antimicrobial agents is the reduction of systemic circulation—a benefit particularly valuable for amphotericin B, which may be nephrotoxic. Nonetheless, toxicities, including the theoretical risk of systemic effects, may still occur with aerosolized administration. With the current dearth of safety and tolerability data, caution should be used when employing aerosolized delivery of anti-infective agents. Caution is particularly important when special formulations for aerosolization are unavailable, as illustrated by two fatalities surrounding the nebulization of colistimethate and zanamivir inhalation powder, incidents that prompted the US Food and Drug Administration to issue an alert to clinicians [51] and a MedWatch safety report [52] respectively. These deaths were attributed to pulmonary injury resulting from increased colistin concentrations caused by prolonged storage (longer than 24 h) of the premixed colistimethate solution, and to obstruction of the ventilator created by lactose contained in the zanamivir nebulizing solution.

The intensity of adverse effects associated with the use of aerosolized amphotericin B (including the liposomal formulations) ranges from mild to severe and may occur with limited exposure, such as once-weekly dosing [53••]. The most common adverse events are local pulmonary effects including cough, decline in pulmonary function tests, and chest tightness [54, 55]. Cough may occur with all aerosolized amphotericin B formulations, including AmBd, ABLC, and L-AmB [6, 45, 55]. In addition, decreases in both the forced expiratory volume and forced vital capacity may occur with aerosolized ABLC [45]. Most of these side effects are mild and result in nominal drug discontinuations. However, bronchoconstriction was reported in one patient who received nebulized AmBd [47]. The administration of a bronchodilator within 15 min before use of the aerosolized antimicrobial may prevent bronchospasm, especially in smokers and asthmatics [56].

Other adverse effects reported with the nebulization of amphotericin B include nausea, vomiting, taste disturbances, tongue numbness, and exacerbation of heart failure [50, 53••]. Though data from the majority of experiences report no systemic exposure, there are reports of trace amounts of amphotericin B in the serum following aerosol administration [31, 54]. Nonetheless, the main adverse events are pulmonary, and the clinical relevance of drug detection in the serum remains unknown.

Several studies have compared safety outcomes between the different formulations of amphotericin B. More adverse events have been reported with AmBd than with ABLC, although these have not significantly increased the need for drug discontinuation [4]. Comparable adverse events were reported in similar proportions of patients receiving AmBd and L-AmB [54]. AmBd may have a detrimental effect on pulmonary surfactant function, possibly resulting from the detergent effect of the deoxycholate rather than as a direct effect of the amphotericin [25]. This effect has not been evident with the lipid formulations.

Conclusions

Current clinical evidence for the use of aerosolized delivery is limited to amphotericin B products for prophylaxis against invasive pulmonary aspergillosis in patients with hematologic malignancies or lung transplantation. Based on conflicting results from clinical trials on efficacy and a lack of safety data, the routine use of aerosolized delivery cannot be recommended. Further research with well-designed clinical trials is necessary to elucidate the therapeutic role of aerosolized delivery of antifungal agents, as well as the associated risks.

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- •• Of major importance

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