Original article

Safety and Usefulness of Nebulized Liposomal Amphotericin B: Systematic Scoping Review

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Abstract

Purpose: Invasive fungal infections potentially result in fatal outcomes in immunocompromised hosts. Compared to intravenous administration, a nebulization therapy can achieve a high concentration of drug delivered in the respiratory tract, without a systematic absorption. We herein summarized the study findings on the safety and clinical utility of nebulized liposomal amphotericin B therapy. **Methods:** According to the PRISMA Extension for Scoping Reviews, we performed a search on MEDLINE and EMBASE for articles with relevant keywords, including "inhaled liposomal amphotericin B", "nebulized liposomal amphotericin B", or "aerosolized liposomal amphotericin B", from the inception of these databases to August 31, 2022. **Results:** Of the 172 articles found, 27 articles, including 13 case reports, 11 observational studies, and 3 clinical trials, were selected. Generally, findings showed that nebulized liposomal amphotericin B treatment appeared to be safe and without severe adverse effects. We found an accumulated evidence for the safety, tolerability, and effectiveness of nebulized liposomal amphotericin B prophylaxis among lung transplantation recipients; however, a randomized controlled study has yet to be reported. Data on hemato-oncological patients are relatively scarce; however, a randomized controlled study suggested the prophylactic effect of nebulized liposomal amphotericin B on invasive pulmonary aspergillosis. Observational and randomized controlled studies to evaluate therapeutic efficacy of the nebulized liposomal amphotericin B therapy have not been performed. **Conclusion:** In conclusion, we found increasing evidence for the effectiveness of the inhalation therapy among patients after lung transplantation and with hemato-oncological diseases.

Introduction

Invasive fungal infections yield high mortality rates among patients, and various preventive and therapeutic strategies have been established [1]. Among the available anti-fungal agents, amphotericin B has the most broad-spectrum activity with accumulated data, among which three distinct forms are clinically available; amphotericin B deoxycholate (ABD), liposomal amphotericin B (LAB), and amphotericin B lipid complex [2]. ABD has long been administered to patients as a conventional amphotericin B agent. However, it causes intensive nephrotoxicity when administered intravenously, and lipid-form drugs have been developed as alternatives and are clinically used worldwide [2].

Although the intravenous administration of ABD is limited with respect to continuation due to its nephrotoxicity, it has been used for inhalation therapy as prophylaxis especially after lung transplantation [3]. Since after 2000, many research studies have indicated the clinical utility of prophylactic administration of nebulized ABD in lung transplant patients [4-6]. However, the supply chain problem has caused a shortage of ABD in Japan, and an alternative prophylaxis is tentatively needed. In such a situation, we found that clinical feasibility of nebulized LAB (n-LAB) therapy was well described in an observational study from two organ transplantation centers in Spain [7]. The study also showed the effectiveness and convenience of n-LAB prophylaxis in preventing *Aspergillus* infection among patients after lung transplantation.

Through a further literature search, we noticed there was no solid evidence in this field. Therefore, we aimed to summarize the available evidence of the clinical utility and safety of n-LAB therapy based on the systematic scoping review of the literature.

Methods

Study Design

We performed a systematic scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for scoping reviews (PRISMA-ScR) [8, 9]. **Appendix 1** is PRISMA-ScR Checklist of the present study.

Search Strategy

MEDLINE and EMBASE search were conducted for all peer-reviewed articles from inception to August 31st, 2022. We employed no filters for study design and language. Additional relevant articles were screened along with the reference lists of all articles that satisfied the eligibility criteria. The search strategy involved the use of relevant keywords, including "inhaled liposomal amphotericin B", "nebulized liposomal amphotericin B", or "aerosolized liposomal amphotericin B". Two authors (HH and YN) conducted the search independently. See **Appendix 2** for details of the search terms.

Eligibility Criteria

The criteria for the inclusion of articles were as follows:

1) Articles describing the any form (prevention or treatment) of the clinical use of n-LAB

2) Randomized controlled trials, case-control studies, cohort studies (prospective or retrospective), cross-sectional studies, case series, and case report

The exclusion criteria were as follows:

1) *in vitro* or animal experiment, conference abstracts, review articles, guidelines, and commentaries.

Study Selection, Data Extraction, and Definition

HH and YN assessed selected articles for full-text assessment independently, and those considered eligible for this study were evaluated comprehensively. We used a standardized data collection form that followed the PRISMA and Cochrane Collaboration guidelines for systematic reviews to obtain the following information from each study: *name of the first author, year of publication, country of origin, study designs, aim of the study, case or study population, regimen of n-LAB, comparative groups, key findings, and limitations.*

Results

Search Results and Study Selection

Figure 1 illustrates a PRISMA flow diagram that depicts the process of identification, screening, eligibility, and inclusion or exclusion of the studies. The initial search of MEDLINE and EMBASE databases yielded 42 and 130 articles, respectively. Of these, 38 duplicate studies were removed.

Subsequently, 134 articles were screened based on their relevance and type of article, and 62 articles that were either *in vitro* or animal experiment or conference abstracts, were excluded from the study. Ultimately, 72 articles were evaluated for full text review for study inclusion per our eligibility criteria; a total of 28 reviews or guidelines, and 17 articles with irrelevant topics were excluded. Finally, 27 articles with 13 case reports and/or case series, 11 observational studies, and 3 clinical trials were selected for the review.

Description of Case Reports and Case Series

Table 1 summarized the main characteristics of case reports and/or case series from the scoping review [10-22]. Since 2007, there were 13 clinical reports, and many of them were from European countries, such as Spain, France, and Italy. The n-LAB therapy was administered for therapeutic purpose in 11 reports, prophylactic purpose in 1 report, and both in 1 report. The therapeutic n-LAB targeted refractory cases of invasive aspergillosis in 6 reports [10,12,13,15,21,22], allergic bronchopulmonary aspergillosis in 3 reports [14,15,19], non-*Aspergillus* mold infections in 3 reports [16-18], and leishmaniasis in 1 report [20]. All six reports describing the use of n-LAB for invasive pulmonary aspergillosis suggested preferable conclusions. In addition, n-LAB could serve as an alternative therapeutic approach to refractory ABPA cases [14,15,19]. The n-LAB was considered to be available for invasive rare mold infections as well as *Aspergillus* infections [16-18]. The administration regimen of n-LAB varied among the reports, ranging from approximately twice daily (15 to 25 mg each) to twice or thrice weekly (20 to 50 mg each).

Description of Observational Studies

Overall, 11 observational studies were identified (**Table 2**) [7,23-32]. Eight studies were single-centered and two were double-centered. There was only one multi-centered study. All the studies, eight of which were performed among lung transplant patients, evaluated the use of n-LAB as prophylaxis [7,23-26,28-30]. The first two observational studies found n-LAB to be safe and well tolerated as ABD nebulization [23,24]. Particularly, Monforte *et al.* provided evidence for the safety and effectiveness of n-LAB in lung transplantation recipients (LTR), based on the following n-LAB regimen; 25 mg 3 times per week up to day 60 post-transplantation, 25 mg once per week between

days 60 and 180 after transplantation, and 25 mg once every 2 weeks for life after transplantation. In 2009 [25], they demonstrated that amphotericin B concentration remained high in the lower respiratory tract even two weeks after the administration of a 25 mg dose of n-LAB and was absorbed from the respiratory tract into serum in only 1 of 27 LTRs. Furthermore, the patient's respiratory function did not change after the initiation of n-LAB. Then in 2010 [7], compared with historical LTR controls who received ABD nebulization, they found that respiratory colonization of *Aspergillus* species, development of invasive aspergillosis, and incidence of bronchospasm were not significantly different among LTRs receiving n-LAB. Moreover, in a small but comparative study with and without the administration of n-LAB, they concluded that prophylactic n-LAB was not associated with changes in the lipid content of pulmonary surfactant [26]. Subsequently, non-comparative studies suggested that, although prolonged administration of n-LAB prophylaxis is tolerable and can be used to prevent *Aspergillus* infection in LTR, detections of *Aspergillus* species and non-*Aspergillus* mold with reduced susceptibility to amphotericin B increased [28,29]. In addition, the clinical utility of n-LAB among patients with hemato-oncological diseases was demonstrated by another research group [27]. According to this case-control study, the administration of n-LAB (12.5mg twice weekly) successfully reduced invasive pulmonary aspergillosis, the total cost of treatment, and the need for the administration of systematic antifungal agents, without increased incidence of serious adverse events related to the inhalation, in patients with acute myeloid leukaemia, myelodysplastic syndrome, and chronic myeloid leukaemia.

Description of Clinical Trials

We found three clinical trials in past studies (**Table 3**): (i) a randomized, double-blind, placebo-controlled trial (phase III clinical trial) [33], (ii) a secondary analysis of the clinical trial [34], and (iii) a prospective case-control study (Phase II clinical trial) [35]. The well-designed, randomized controlled trial corroborated that n-LAB prophylaxis significantly reduced the incidence of invasive pulmonary aspergillosis in patients with prolonged neutropenia due to hemato-oncological diseases [33], without deteriorating their pulmonary function [34]. One clinical trial reported that 42% of patients found n-LAB prophylaxis to be unpleasant mainly because it induced coughing and had an unpleasant taste. However, 1-year survival rates were ameliorated among patients receiving n-LAB

prophylaxis [35]. There was no clinical trial aimed at evaluating the prophylactic effectiveness of n-LAB in LTR.

Discussion

We conducted a systematic scoping review to uncover clinical evidence regarding the performance of n-LAB therapy. n-LAB was reportedly effective in both therapeutic and prophylactic administration. Most of the case studies focused on the use of n-LAB as a topical treatment of respiratory fungal infections, such as invasive aspergillosis, allergic bronchopulmonary aspergillosis, and non-*Aspergillus* mold infections. Despite a potential publication bias, n-LAB treatment appeared to have certain therapeutic effects without serious adverse effects. Of the 11 observational studies, 8 were single-centered, 5 of which focused on LTR. We found an accumulated evidence regarding the safety, tolerability, and effectiveness of n-LAB prophylaxis for LTR. Data for hemato-oncological patients are relatively scarce; however, a randomized controlled study (phase III clinical trial) clearly suggested the prophylactic effect of n-LAB against invasive pulmonary aspergillosis among such vulnerable populations [33]. A recent exploratory network meta-analysis suggested that n-LAB would be the most effective prophylactic approach in LTR [36]. However, we found that randomized controlled evaluations of the prophylactic effectiveness of n-LAB in LTR are lacking, which presents scope for further study. Furthermore, neither observational nor randomized controlled studies regarding its therapeutic efficacy have been performed. Future studies should focus on invasive aspergillosis and allergic bronchopulmonary aspergillosis, considering the incidence and impact of the diseases.

Safety should be prioritized when considering further clinical indications of n-LAB. Generally, in the case of applying an injectable formulation as an inhalant, several precautions should be taken; (i) preservatives (nothing added), (ii) osmolality (being not hyperosmotic), (iii) power of hydrogen (pH being neutral), (iv) ionic composition (having as appropriate), and (v) toxicity to respiratory tissues or cells (ensuring treatment is not cytotoxic to the respiratory epithelial cells and alveoli). We found that the safety and tolerability of n-LAB have been studied in-depth in the past two decades. Studies have reported that although up to nearly 40% of patients receiving n-LAB complained of irritation [23,29,33,35], amphotericin B was not measureable in serum samples and respiratory

function was not adversely affected [25,34]. No serious adverse effect after n-LAB was reported; therefore, n-LAB therapy can be extensively applied clinically for both prophylactic and therapeutic purposes.

The inhalation regimen of n-LAB varied among the studies. Maximum dosages of n-LAB were 50 mg per dose, but most cases or studies administered 25 mg per dose of n-LAB. For prophylactic purposes, 12.5 mg per dose of n-LAB may be feasible. For treatment, patients received different dosages of n-LAB with frequencies ranging from twice daily to twice or thrice weekly. As reported, because amphotericin B can be retained in the respiratory tract at therapeutic concentration levels for at least two weeks [25], frequent administration would not be necessary. Future studies with more optimized designs should establish the appropriate regimen of n-LAB.

Presently, a nebulization technology for amphotericin B has been steadily improved. With an increased drug concentration at a local infectious site and reduced pharmaceutical toxicity, liposomalization has been corroborated to be a safe and applicable method for a wide range of antimicrobials [37, 38]. The feasibility and usefulness of inhaled liposomal antimicrobials for pulmonary infections are well summarized in a recent review article, in which amphotericin B, as well as several antibiotics such as tobramycin, amikacin, and ciprofloxacin, are reportedly productized [39]. A carbohydrate-based amphotericin B dry powder inhaler formulation, in combination with cyclodextrin, leucine, and mannose in appropriate amounts, is recently introduced by Pablo et al., which showed greater stability at ambient and refrigerated temperature, longer retention times following intratracheal *in vivo* administration, and an increased macrophage uptake [40]. Other researchers have developed inhalable proliposomal microparticles/nanoparticles of amphotericin B, with lung surfactant-mimic phospholipids [41]. They used the Handihaler® (Boehringer Ingelheim, Ingelheim, Germany), the FDA-approved dry powder device, which is thus easily applicable in clinical settings. Further investigations will seek the potential and development of the nebulizing method of amphotericin B, a promising, broad-spectrum antifungal agent.

The following limitations of this review should be addressed. We screened MEDLINE and EMBASE for the searching terms to thoroughly include relevant articles. However, we may have failed to identify some clinical data regarding the use of n-LAB among patients. n-LAB has been successfully administered to patients for both therapeutic and prophylactic purposes, but a publication

bias should be considered, particularly for case reports or case series. Only half of the observational studies had comparative groups, and there were only three clinical trials. This fact indicated the need to perform studies with more optimized designs in this subject, such as a prospective case-control study or randomized controlled study. Additionally, amount of the inhaled drugs actually conveyed to the lower respiratory tract depends on the nebulizing method used [42], which may heavily influence the safety and efficacy of n-LAB therapy. Despite these concerns, our review of the existing evidence on the efficacy of n-LAB will be beneficial to clinicians, particularly in the fields of lung transplantation and hemato-oncology.

Collectively, evidence of the safety and clinical effectiveness of n-LAB has been gradually accumulated since 2007. However, many are in the form of case reports, case series, or non-comparative observational studies. Future studies that can yield additional sufficient evidence are required to allow for the approval of n-LAB as an insurance treatment and have it incorporated into the recommended routine care of immunocompromised patients.

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Author contributions

HH conceived the study, searched related literature, and drafted the manuscript. YN searched related literature, assessed the quality of the studies, and revised the manuscript. FO supervised the study.

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Figure 1. Flow of the study