

Role of inhaled amphotericin in allergic bronchopulmonary aspergillosis

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:: Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder caused by immune reactions mounted against the ubiquitous fungus *Aspergillus fumigatus*. The disease clinically manifests with poorly controlled asthma, hemoptysis, systemic manifestations like fever, anorexia and weight loss, fleeting pulmonary opacities and bronchiectasis. The natural course of the disease is characterized by repeated episodes of exacerbations. Almost 30-40% of the patients require prolonged therapy, which currently consists of corticosteroids and anti-fungal azoles; both these agents have significant adverse reactions. Amphotericin B administered via the inhaled route can achieve a high concentration in the small airways with minimal systemic side-effects. Nebulized amphotericin B has been used in the management of invasive pulmonary aspergillosis. The aim of this review is to study the utility of inhaled amphotericin in ABPA.

Keywords: ABPA, ABPM, allergic bronchopulmonary mycosis, amphotericin, *Aspergillus*, asthma, azoles

:: Introduction



Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity response to fungal antigens released by *Aspergillus fumigatus* colonizing the tracheobronchial tree of patients with asthma and cystic fibrosis (CF). ^[1] The disorder clinically presents as difficult-to-control asthma, recurrent pulmonary infiltrates and bronchiectasis. ^[2] The diagnosis of ABPA is based on a combination of various clinical, immunological and radiological criteria. These criteria have been recently revised to make the diagnosis simpler and more uniform. ^[2] The course of this disease is interjected by recurrent episodes of exacerbations marked by clinico-radiological deterioration. ^{[3],[4],[5],[6],[7]} Although the disorder was initially described in 1952, ^[8] the treatment remains unclear especially in

those with recurrent exacerbations. The therapy of ABPA targets two possible pathogenetic pathways. The anti-inflammatory agent (glucocorticoids) controls the inflammation and immunological phenomenon while the antifungal drugs (azoles, amphotericin B) target the antigen burden due to reduction in airway colonization with the organism. ^[9]

Prolonged use of oral steroids can cause several side-effects (like hyperglycemia, Cushing's disease, osteoporosis and others), while the use of azoles may be associated with various drug interactions, adrenal suppression and hepatotoxicity. ^[9] This has led to a search for alternate agents like inhaled amphotericin B and monthly methylprednisolone pulses, ^{[10],[11]} with an aim to reduce the duration and dosage of both corticosteroids and azoles. The use of an inhaled route is particularly attractive as it can deliver a high concentration of the therapeutic agent at the intended site with minimal adverse events. The aim of this review is to study the utility of inhaled amphotericin in ABPA.

Literature search

We searched the PubMed and EmBase databases using the following free text terms: (aerosol * amphotericin OR nebuliz * amphotericin OR inhal * amphotericin OR nebulis * amphotericin) AND ("abpa" OR "allergic bronchopulmonary aspergillosis" OR "allergic bronchopulmonary mycosis" OR "abpm"). In addition, we reviewed data on file.

Pharmacology of amphotericin B

Amphotericin was isolated in 1956 and is currently the broadest spectrum antifungal drug available. Amphotericin B is polyene produced by *Streptomyces nodosus*. At neutral pH, amphotericin B is insoluble in water but gets dissolved in 5% dextrose in water. When adjusted to a pH of 5.0-7.5, it appears as a clear yellow colloidal micellar solution. Conventional amphotericin B (50 mg) has a detergent (deoxycholate, 41 mg) and a buffer (sodium phosphate, 25.2 mg) for its preparation. The use of amphotericin B deoxycholate (ABDC) is associated with various side-effects, both acute (fever, chills, rigors, anaphylaxis, cardiac arrhythmias, liver failure) and chronic (renal tubular acidosis, interstitial nephritis, hypokalemia and hypomagnesemia). To overcome some of these side-effects, newer lipid preparations are available. ^[12]

Amphotericin is a hydrophilic compound, but it can be incorporated into the liposomal bilayer, which reduces its toxicity. Liposomes are microscopic vesicles containing multiple concentric lipid bilayers; the vesicles can be unilamellar or multilamellar. Multilamellar liposomes are most commonly used to incorporate therapeutic agents. The multilamellar vesicle consists of two compartments, a central aqueous layer and a peripheral multi-layer lipid compartment on either side. ^[13] Organs rich in cells from the reticuloendothelial system (lungs, bone marrow, liver and spleen) preferentially take up liposomes. ^[14] Incorporation of sterols like ergosterol and cholesterol into liposomes makes the liposome more rigid and stable. However, in case of amphotericin B, ergosterol incorporation decreases antifungal activity due to tight drug sterol binding, impeding drug exchange with fungal membranes, and hence reduced activity. ^[14] The reduced toxicity of liposomal amphotericin has been attributed to selective delivery of amphotericin B to the fungal membranes. This is supported by a study in which liposomal amphotericin B was less toxic to erythrocytes than to fungal cells. ^[15] Amphotericin B intralipid formulation, lipid-stabilized amphotericin B, mixtures of amphotericin B and cholesterol or lipoprotein are other methods of drug delivery that decrease toxicity. ^[12]

Besides drug modification, various routes of delivery have been developed for direct delivery and reduction in side-effects of amphotericin B. Intranasal administration of amphotericin B has been shown to reduce the colonization of nasal cavity with *Aspergillus* in patients with leukemia patients.

[16] Initial studies of inhaled amphotericin B were performed in animals, which demonstrated substantial lung tissue concentration with minimal systemic levels. [17],[18] *In vitro* studies have demonstrated that the deoxycholate component of ABDC may cause changes in pulmonary surfactant activity, which can lead to alteration in pulmonary function. [19] In this regard, lipid formulations of amphotericin B, namely liposomal amphotericin B (LAMB) and amphotericin B lipid complex (ABLC), are better than ABDC, with longer pulmonary retention and no significant effects on lung surfactant.

Pharmacokinetics of inhaled amphotericin B

To be effective, an inhaled drug should be delivered in quantity sufficient enough to achieve a therapeutic level. Also, the aerosol size, concentration needed and nebulizer delivery system need to be optimized. One bench study compared 12 different nebulizer delivery systems for output rates and aerosol size of ABLC, and found that the aerosol size and output could vary by a factor of two with different nebulizers. [20] Only 10-20% of the dose initially prepared and nebulized reached the area of interest. [20] The delivery of inhaled drug may be even lower in diseased lungs due to altered pulmonary ventilation-perfusion relationships. The minimal inhibitory concentration (MIC) for *A.fumigatus* is approximately 0.5mg/L. In a study, nebulization of 30 mg of ABDC (5mg/mL in 15-20 min) achieved bronchoalveolar lavage fluid (BALF) amphotericin B concentrations of 0.68 ± 0.36 mg/L and 0.5 ± 0.31 mg/L in the upper and lower lobes, respectively. [21] Similar results were seen in another study that demonstrated a mean concentration of 1.46 mg/L and 15.75 mg/L in bronchial washings and BALF, respectively. [22] In fact, administration of aerosolized ABLC 1 mg/kg every 24 h for four days in lung transplant recipients achieved BALF concentrations above the MIC of *Aspergillus* for up to 168 h after the last inhaled dose. [23]

Serum levels of amphotericin B attained after nebulization are negligible. One study found a peak serum amphotericin B level of 0.025 mg/L after inhalation of 5 mg of ABDC (1mg/mL), which is roughly 20 times less than the 0.5-2 mg/L steady state concentration achieved after an intravenous route. [24] In another study, serum levels of amphotericin B were measured three times a week, before and after 1h of administering 10 mg twice daily of inhaled ABDC (1 mg/L in 15-20 min). [25],[26] Of the 168 samples obtained, the levels in 150 (89%) patients were below the lower limit of detection (0.1 mg/L), and in the remaining the levels were below 0.2 mg/L. In a dose-ranging study (5, 10, 15 or 20 mg twice daily), it was found that serum levels of 2 mg/L were achieved if the 20 mg dose was used. These results suggest that there may be a dose-response relation. However, the lung concentrations (and thereby the serum concentrations) of amphotericin B varies depending on the type of nebulizer used and the lung status. Inhaled amphotericin B is likely to be efficacious in the treatment of ABPA as it achieves concentrations in the BALF well above the MIC for *A.fumigatus*. [21],[22] Another advantage is the lack of side-effects as serum levels are maintained well below that associated with toxicity. [24],[25],[26]

Efficacy of Amphotericin B in ABPA

Our database search yielded seven citations (19 patients) that have systematically described the role of inhaled amphotericin in ABPA [Table 1]. Although the use of aerosolized forms of amphotericin B has been reported in the past, [27],[28],[29] it was used in a half-hearted manner with unspecified dose and duration.

Author	Year of publication	AMB formulation	Dose	Duration (in months)	Nebulizer	No. of Patient	Outcome
Casey <i>et al.</i> ^[30]	2002	ABDC	16-40 mg/day in divided doses	4 months	ND	1	ABPA in LT
Suzuki <i>et al.</i> ^[31]	2002	ABDC	2.5mg/mL TDS	ND	ND	1	ABPA in CF
Tiddens <i>et al.</i> ^[32]	2003	LAMB	50 mg once a week (8 mL over 150 min)	ND	Halolite	5	ABPA in CF
Laoudi <i>et al.</i> ^[33]	2008	ABDC and inhaled budesonide	5 mg BD	6 months	ND	3	ABPA in CF
Hayes <i>et al.</i> ^[34]	2010	ABDC	10 mg BD (2.5 mg/mL)	9 months	ND	1	ABPA in CF
Proesmans <i>et al.</i> ^[35]	2010	ABDC (3); ABLC (4)	ABDC 20 mg thrice weekly (1 mg/mL); ABLC 50 mg (5 mg/mL) twice weekly	ABDC (12 months); ABLC (28 months)	PAR1 turboboy or Aeroneb Go	7	ABPA in CF
Godel <i>et al.</i> ^[36]	2012	LAMB	LAMB 25 mg twice weekly till cessation of steroids followed by 25 mg once a week for 6 months	8 months	ND	1	ABPA with asthma

ABDC – Amphotericin deoxycholate; ABLC – Amphotericin B lipid complex; BD – Twice daily; CF –Cystic fibrosis; FEV1 – Forced expiratory volume in the first second; LAMB –Liposomal amphotericin B; LT –Lung transplantation; ND – Details not available; TDS – Three times daily

Casey *et al.* were the first to systematically describe the use of inhaled ABDC in a 26-year-old double lung transplant recipient who presented with ABPA 5 months after transplant.^[30] The patient was treated with oral prednisolone and itraconazole (600 mg/day). Inhaled ABDC was administered after persistent need for oral corticosteroids. There was improvement in lung function, reduction in dose of oral steroid and cessation for the need of itraconazole. Inhaled ABDC was well tolerated and the benefits were sustained 9 months after stopping inhaled amphotericin. Suzuki *et al.* used inhaled ABDC in a 9-year-old boy with CF and ABPA.^[31] The child presented with fleeting opacities and was managed with oral prednisolone (1 mg/kg) and inhaled ABDC 2.5 mg thrice daily (2.5 mg/mL). Oral prednisolone could be tapered and stopped after 7 weeks, with no further exacerbations and maintenance of clinical stability. Tiddens *et al.* investigated the role of LAMB nebulized once a week in five patients with CF-related ABPA.^[32] Four patients had developed Cushing's syndrome due to high-dose corticosteroids and one patient had progressive *Mycobacterium avium* *sp.* *intracellulare* (MAC) infection, requiring steroid withdrawal. Corticosteroids could be stopped in four patients. One patient relapsed 7 months after stopping LAMB, and was given a repeat course of inhaled LAMB. All the patients tolerated inhaled LAMB, with no deterioration in lung function and oxygen saturation. Laoudi *et al.*^[33] reported successful treatment of three children with CF-associated ABPA using inhaled budesonide and nebulized ABDC. There was improvement in hypoxemia, lung function (forced expiratory volume in the first second [FEV1]), blood eosinophil counts, total and specific IgE antibodies to *A.fumigatus* and disappearance of precipitins to *A.fumigatus*. This was the first report on the combined use of inhaled budesonide and amphotericin B. None of the patients developed any side-effects. Hayes *et al.*^[34] reported a 14-year-old female with end-stage CF lung disease and ABPA. Because of the persistent need of high-dose oral corticosteroids, she was treated with nebulized ABDC. There was improvement in lung function; itraconazole was stopped 2 months later and prednisolone was stopped 6 months after institution of nebulized ABDC. There were no reported side-effects associated with nebulized ABDC.

In the largest study on the use of inhaled amphotericin B till date, Proesmans *et al.* described their experience with seven children (age, 5.5-11 years) with difficult-to-treat ABPA and CF. ^[35] Inhaled amphotericin was considered if there was insufficient response to corticosteroids and itraconazole, frequent relapse of ABPA during/after steroid taper despite itraconazole, failure to taper systemic steroids or intolerance to itraconazole. Inhaled ABDC was first administered as a test dose and, if tolerated, the therapy was given thrice a week. In case of intolerance to ABDC (cough, wheeze and shortness of breath), ABLC was used. The primary endpoint was discontinuation of systemic corticosteroids, without ABPA relapse for 12 months, after stopping steroids. Five of the seven patients achieved disease control and systemic steroids could be stopped in them. The average duration of ABPA relapse-free period was 18.8 months (range, 9-29 months). Most of the patients tolerated the treatment with inhaled ABDC and reported mild symptoms like cough or wheeze. None of the patients reported any adverse effects when they were switched over to nebulized ABLC.

Recently, Godet *et al.* described a 67-year-old lady, a case of difficult-to-treat ABPA complicating asthma with standard treatment regimen. The patient was initially treated with steroids and nebulized LAMB, with the latter continuing after cessation of steroids. There was no relapse after 12 months of stopping prednisolone. ^[36]

The use of inhaled amphotericin B may have several beneficial effects in the management of ABPA, especially in patients who are glucocorticoid-dependent and/or fail to achieve disease control with conventional therapy. By directly targeting the site of involvement, inhaled amphotericin delivers adequate drug at the required site. However, the data are currently sparse and because of the lack of control group, it is not clear whether patients actually responded to amphotericin B or were just delayed (or spontaneous) remissions, which are so characteristic of ABPA. Also, majority of these patients were of the pediatric age group, and all had underlying CF. Only one adult patient with asthma and ABPA has been described in the literature, who was successfully treated with inhaled amphotericin B. ^[36]

Of the 19 patients described, good clinical response was seen in 17 patients. In 16 patients, oral corticosteroids were tapered and stopped, whereas in one patient the dosage was significantly reduced. In all the patients, inhalational amphotericin B was considered once conventional therapy with oral steroids and itraconazole had failed to control the disease activity. Once the disease was controlled, most patients remained in remission even 1 year after stopping steroids, and the disease could be controlled with inhaled amphotericin B as a single agent alone. Only minimal side-effects in the form of cough or dyspnea were reported. *In vitro* studies suggest that the deoxycholate component of ABDC may be associated with surfactant dysfunction, and hence some side-effects. ^[19] However, in most of the reports, ABDC was the initial agent of choice; liposomal preparations (LAMB or ABLC) were used only in those who could not tolerate ABDC or who needed prolonged inhalational therapy.

Practical considerations on the use of inhaled amphotericin

In a resource-limited setting such as India, it may not be feasible to use LAMB or ABLC due to cost considerations, and our review suggests that ABDC may be also be used effectively ^[Table 2]. Reconstituted solution of ABDC can be stored for 24 h at ambient temperature and for 1 week at 2-8°C, with minimal loss of potency. On the other hand, reconstituted LAMB and ABLC can be stored for a maximum of 24 and 48 h, respectively, at 2-8°C. The cost of 50 mg vial of ABDC is 250 Indian rupees, while the price of LAMB and ABLC is 6000 and 3500 Indian rupees, respectively. At our institute, we use inhaled ABDC (5mg/mL) at a dosage of 10 mg twice a day three times in a week along with inhaled budesonide at a dosage of 0.5-1 mg twice daily.

Formulation	Carrier	Colloidal type	Size (µm)	Dosage
ABDC	Deoxycholate	Micelle	0.035	10 mg twice daily three times in a week (5 mg/mL over 10-15 min)
LAMB	PC/DSPG/Chol	Liposome	0.08	50 mg in two divided doses in a week (5 mg/mL) over 10-15 min
ABLC	Phospholipids	Lipid ribbon	1.6-11	50 mg in two divided doses in a week (5 mg/mL) over 10-15 min

ABDC – Amphotericin deoxycholate; ABLC – Amphotericin B lipid complex; Chol – Cholesterol, DSPG – Distearoyl-phosphatidylglycerol; LAMB – Liposomal amphotericin B; PC –Phosphatidylcholine

Table 2: Various formulations of amphotericin B and their recommended dosage for inhalation therap (adapted from^[35])

Future directions

Currently, we are recruiting patients in a randomized controlled trial, investigating the role of inhaled amphotericin B in maintaining remission in ABPA (clinicaltrials.gov: NCT01857479). Patients with ABPA who have entered into remission after treatment with glucocorticoids are being randomized to inhaled amphotericin B plus budesonide or inhaled budesonide alone. The primary endpoint is time to first relapse. The results of this trial will hopefully help elucidate the role of inhaled amphotericin B in maintenance of remission in patients with ABPA.

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