

Aerosolized Amphotericin for the Treatment of Allergic Bronchopulmonary Aspergillosis

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Summary. Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction to *Aspergillus fumigatus* that occur frequently in patients with cystic fibrosis (CF). Recurrent episodes of bronchial obstruction, inflammation, and mucoid impaction occur in ABPA and results in bronchiectasis, fibrosis, and respiratory failure. The treatment of ABPA includes corticosteroids to reduce the acute inflammation and itraconazole to reduce the fungal colonization load in order to reduce lung injury. This case discusses the successful use of aerosolized amphotericin B for the treatment of ABPA in a 14-year-old patient with CF listed for lung transplant. The patient required fewer hospitalizations, and both oral corticosteroids and anti-fungal therapy were eventually stopped. **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

Key words: aerosolized; *Aspergillus fumigatus*; inhaled; amphotericin B; cystic fibrosis; allergic bronchopulmonary aspergillosis.

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) occurs in patients with cystic fibrosis (CF) when *Aspergillus fumigatus* spores are inhaled and colonize the lower airways. It can be difficult to establish a diagnosis of ABPA in patients with CF due to overlapping clinical, radiographic, and immunologic features; however, early identification and treatment of the disease can improve symptoms, pulmonary function, and outcomes. The prevalence of ABPA in CF varies between 2% and 15% with a peak occurring during the late teen and young adult years.^{1–7}

The pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) is not completely understood. Skin testing demonstrates a high sensitization rate for *Aspergillus*, but there is no relation between the intensity of exposure to the airborne spores and rates of sensitization.⁸ Sensitization to fungi is high in childhood and declines rapidly with age, suggesting that younger children may be less proficient in clearing fungi from the airways.⁹ Exposure to fungal spores or mycelial fragments results in the formation of IgE and IgG antibodies in patients with cystic fibrosis (CF).^{10,11} Despite this vigorous immunological response in ABPA, the fungus is still able to colonize the lower airways and cause clinical symptoms with the eventual development of bronchiectasis and destruction of lung parenchyma. From a pathological standpoint, ABPA is characterized by mucoid impaction and eosinophilic

pneumonia, which may lead to bronchiolitis obliterans, granulomatous bronchiolitis, bronchiectasis, and pulmonary fibrosis.^{12–14} There are limited therapies available

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for the treatment of ABPA with those treatment options having adverse side effects. A recent review article was published by Kuiper and Ruijgrok that reported the use of aerosolized amphotericin was encouraging and should be considered in patients with ABPA with corticosteroid dependence.¹⁵ The limiting factor is that there is no standard dose for amphotericin with several different administration techniques used by investigators who have published on the inhalation of amphotericin for treatment.¹⁵ We present a case of ABPA in an adolescent female patient with end-stage lung disease who had significant improvement in symptoms and reduction in other therapy with aerosolized amphotericin.

CASE REPORT

A 14-year-old female with end-stage CF lung disease (sweat chloride 94 mEq/L, $\Delta F508$ homozygous), who was listed for lung transplantation 6 months earlier, was hospitalized for the third time over the previous 2 months due to progressing dyspnea and worsening cough and sputum production. The patient also had weight loss of 3 lbs and worsening fatigue. She only required one hospitalization during the 6 months prior to being listed for lung transplantation. Her supplemental oxygen requirement had also increased from a baseline of 3 to 6 L/min via nasal cannula. Her pulmonary function declined from a baseline of forced vital capacity (FVC) 1.21 L (41% predicted) and forced expiratory volume in 1 sec (FEV₁) 0.80 L (30% predicted) to FVC 0.82 L (27% predicted) and FEV₁ 0.49 L (18% predicted). Chest X-ray demonstrated a slight increase in perihilar bronchial thickening and severe bronchiectasis without change. For the past 12 months, her sputum culture isolated *A. fumigatus*, while two mucoid strains of *Pseudomonas aeruginosa* were isolated in the past 3 years. One *P. aeruginosa* strain was pan-sensitive, and the other strain was pan-resistant. Intravenous (IV) therapy started for the acute exacerbation was cefepime 6 gm continuous infusion over 24 hours and tobramycin 240 mg once daily based on previous synergy studies. Upon admission, her IgE level increased from 40 to 3,470 IU/ml (normal range 0–120 IU/ml) with an immediate wheal-and-flare reaction to a skin prick test for *A. fumigatus* antigen at 5 mm. Serum IgE antibodies for *A. fumigatus* by radioallergosorbent test (RAST) was elevated at 2.38 kU/L (normal range < 0.35 kU/L), which is a high positive response. The anti-*A. fumigatus* IgE index was 16.6, and the IgG index was 2.94. Serologic evaluation demonstrated a positive precipitin reaction against *A. fumigatus*. The patient was diagnosed with ABPA and was treated with IV methylprednisolone 30 mg every 6 hr and itraconazole 200 mg orally twice daily along with continuation of the IV antibiotics. On hospital day 10, she was discharged home

to complete 14 days of IV antibiotics along with prednisone 30 mg twice daily and itraconazole 200 mg twice daily. As an outpatient 1 month later, the patient did not tolerate a reduction in the prednisone from 30 to 25 mg daily, requiring re-hospitalization 2 days after the reduction in dose. During this particular 5-day hospitalization, she was treated only with IV methylprednisolone 30 mg every 6 hr for the first 3 days with a change to prednisone 30 mg twice daily. A 6-min walk test was performed the day prior to discharge that demonstrated oxygen saturation at rest of 94% on 3 L/min with a total walk distance of 625 feet with a reduction of oxygen saturation to 89%, despite being fully treated with systemic corticosteroid therapy and itraconazole. In an effort to reduce the corticosteroid dose since she was actively listed for lung transplantation with concerns regarding wound healing after surgery, a trial of aerosolized amphotericin was attempted on the day of discharge. The standard IV amphotericin B 5 mg (X-GEN Pharmaceuticals, Inc., Big Flats, NY) was reconstituted in 2 ml of sterile water. A dose of 10 mg was administered twice daily via a Pari LC PlusTM nebulizer and mask. The patient tolerated this inhaled therapy well without any adverse symptoms with improvement in cough and dyspnea. At her next clinic appointment 1 month later, her pulmonary function improved with the FVC and FEV₁ being 41% predicted and 30% predicted, respectively. At the next clinic visit 2 months later, itraconazole therapy was stopped. Prednisone was tapered to 15 mg daily during this 3-month time frame between these two clinic appointments. After 3 months of aerosolized amphotericin, itraconazole was stopped and the prednisone dose was reduced by half.

The patient continued to do well with cough and sputum production being at baseline with no change in her physical examination or pulmonary function. Repeat 6-min walk test demonstrated oxygen saturation at rest of 94% on 3 L/min with improvement in the total walk distance to 878 feet without oxygen desaturation. Serum IgE level was normal at 52 IU/ml. Prednisone was subsequently stopped approximately 6 months after starting aerosolized amphotericin.

For the next 3 months, the patient remained on aerosolized amphotericin as single drug therapy for ABPA without need for hospitalization. Hepatic and renal function tests were assessed on multiple occasions during treatment with aerosolized amphotericin with no abnormalities seen. Her respiratory cultures continued to isolate two mucoid strains of *P. aeruginosa* that have the same susceptibility pattern as previously reported with no further isolation of *A. fumigatus*. Her 6-min walk test demonstrated even further improvement on single drug therapy with oxygen saturation at rest of 94% on 3 L/min with improvement in the total walk distance to 1,227 feet without oxygen desaturation.

DISCUSSION

The treatment of ABPA focuses on controlling acute inflammation and preventing progression of lung injury. The use of corticosteroids is the most common and effective therapy^{16,17} with growing evidence of the benefits of treatment with itraconazole.^{4,18–20} In 2008, the Infectious Diseases Society of America published guidelines²¹ recommending a combination of corticosteroids and itraconazole therapy for ABPA. Commonly, itraconazole is used as a steroid-sparing agent due to the severe metabolic side effects associated with systemic corticosteroids. In a retrospective series of 16 CF patients with ABPA, the use of itraconazole resulted in a 55% reduction in the number of acute ABPA episodes.⁴

There is limited experience with the use of amphotericin by inhalation for the treatment of ABPA. Aerosolized amphotericin was used successfully in a lung transplant recipient who developed acute ABPA 5 months after bilateral sequential lung transplantation.²² This particular patient responded quickly, so prednisone requirement dramatically decreased and itraconazole was eventually stopped.²² More recently, a case series of three children with CF demonstrated improvement with nebulized amphotericin and nebulized budesonide.²³

Another potential therapy that may be beneficial in the treatment of ABPA is omalizumab, which is a humanized monoclonal antibody directed against immunoglobulin-E (IgE). Case reports and series have demonstrated successful outcomes using omalizumab in CF patients with ABPA;^{24–26} however, no definitive clinical trials have been performed to date to truly demonstrate efficacy of treatment with omalizumab.

In conclusion, we report the successful use of aerosolized amphotericin as a single therapy for the treatment of ABPA in an adolescent with end-stage CF, awaiting lung transplantation. Both systemic corticosteroids and itraconazole were stopped without adverse effects or recurrence of symptoms, and there was no need for inhaled corticosteroids. In addition to improvement in clinical symptoms, her functional status improved dramatically as seen on 6-min walk tests with normalization of IgE levels and return of pulmonary function to baseline measurements. To our knowledge, this case is the first to report the improvement of functional capacity as measured with the 6-min walk test in the treatment of ABPA with the aerosolized amphotericin. We believe that research with large, controlled trials is needed to investigate aerosolized amphotericin in the treatment of ABPA as compared to systemic corticosteroids and itraconazole.

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