

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

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Abstract

Mucus plugging is associated with several lower respiratory tract illnesses in the pediatric population. Majority of lower respiratory tract illnesses are treated with supportive care and lacks effective curative options. Dornase alfa, a mucolytic agent often used in patients with cystic fibrosis, was theorized to have benefits in other respiratory conditions such as bronchiolitis, asthma, and atelectasis seen in mechanically-ventilated patients. Clinical studies performed thus far, however, did not show any clinical significance in using this regimen for majority of these indications. The only potential use of dornase alfa is in mechanically-ventilated patients who have developed atelectasis, but 3-7% hypertonic saline should be utilized first due to its reduced cost and its similar efficacy to dornase alfa.

Keywords: Asthma; bronchiolitis; dornase alfa; pediatrics; pulmonary atelectasis

ABBREVIATIONS

CICU- cardiac intensive care unit;

CXR- chest radiographs;

CF- cystic fibrosis;

DNA- deoxyribonucleic acids;

ED- emergency department;

FiO₂- fraction of inspired oxygen;

FEV₁- forced expiratory volume in 1 second;

ICU- intensive care unit;

NICU- neonatal intensive care units;

PaO₂- partial pressure of arterial oxygen;

PCO₂- partial pressure of carbon dioxide;

PIP- peak inspiratory pressure;

PEEP- positive end-expiratory pressure;

PMN- polymorphonuclear neutrophils;

rhDNase- recombinant human dexoyribonuclease;

RSV- respiratory syncytial virus

INTRODUCTION

Respiratory illnesses are among the top 10 diagnoses of emergency department (ED) visits for pediatric patients in the United States and Europe.¹⁻² Twenty five percent of all hospitalization in children younger than 5 years of age was caused by lower respiratory tract infections.³ Potential causes are due to mucus hypersecretions or the inability to clear mucus within the respiratory tract in diseases such as cystic fibrosis, asthma, and bronchiolitis. This problem may in turn lead to the accumulation of mucus production within airways and the development of respiratory symptoms. It has been proposed that mucolytic agents may be

beneficial in patients with mucus overproduction.⁴ The use of mucolytic agents is often seen in patients with cystic fibrosis (CF). However, due to the lack of treatment options for severely-ill patients with other respiratory conditions, this may be an alternative agent beyond supportive care.

Agents that have been shown to aid in mucus clearance include hypertonic saline, N-acetylcystine and dornase alfa.⁵ Each agent works on different components within the mucus to help liquefy and clear the mucus. Dornase alfa (Pulmozyme®) is a mucolytic agent approved by the Food and Drug Administration for the treatment

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

of cystic fibrosis. Dornase alfa is a recombinant human deoxyribonuclease (rhDNase) that essentially works by cleaving deoxyribonucleic acids (DNA) released from degenerating polymorphonuclear leukocytes found within mucus secretions.⁶ Mucus viscosity and elasticity are directly correlated with the amount of DNA content.⁷ Dornase alfa can be administered via nebulization or intratracheally down an endotracheal tube for patients who are on mechanical ventilation. Studies have shown that rhDNase has the ability to reduce viscosity of purulent CF-sputum in a concentration-dependent manner.⁸ There has been much debate on whether rhDNase may be beneficial to patients without cystic fibrosis. Depending on the indications, there are few trials performed thus far to help elucidate the efficacy and use of the medication in this patient population. The aim of this review is to summarize the relevant literature for the use of dornase alfa in pediatric patients with non-cystic fibrotic lung diseases, mainly bronchiolitis, asthma, and atelectasis seen in mechanically ventilated patients.

BRONCHIOLITIS

Bronchiolitis is one of the most common lower respiratory tract infections seen in infants younger than 12 months of age.⁹ Bronchiolitis is usually caused by viruses, respiratory syncytial virus (RSV) being one of the most common organisms seen during the winter months.¹⁰ Each year, this clinical condition results in approximately 3% of infants needing hospitalization and an estimated 500 deaths in the United States.⁹ Similarly, the incidence of hospitalization due to bronchiolitis increased substantially in Europe from 2000 to 2013.² The infection causes damage to the respiratory tract and sloughing of the epithelium lining and cilia. As a result, increase in mucus plugging within the airways can occur.¹¹ First line therapy for bronchiolitis is supportive care with oxygenation, hydration, and reduction of fever.¹² It has been suggested that since bronchiolitis can lead to mucus plugging with DNA present, a logical approach in therapy is to use mucolytic agents like dornase alfa in this patient population.¹³

Two randomized controlled trials were performed to assess the efficacy and safety of dornase alfa in patients hospitalized with RSV bronchiolitis. The first study was a multicenter, randomized, double-blind, controlled trial that included 225 patients younger than 12 months of age proven to have bronchiolitis and require supplemental oxygen.¹⁴ They assessed the efficacy of 2.5mg of rhDNase (2.5mL of 1mg/mL rhDNase) to placebo given twice daily until hospital discharge, discontinuation of supplemental oxygen for at least 12 hours, or until the need of transferring to an intensive care unit (ICU). Baseline characteristics were mostly similar between groups except that there was a significantly lower birth weight in the rhDNase group compared to the control group. The primary objective was mean duration of hospital stay, and the difference was not statistically significant (rhDNase: 4.4 days vs Placebo: 3.8 days; $p=0.11$). Also, no difference was found in the mean duration of supplemental oxygen between the 2 groups (2.6 days vs 2.0 days respectively; $p=0.053$). One potential limitation of the study was that it did not include very sick patients with atelectasis who required ICU admission, a population likely to have more mucus production allowing for potential greater benefit from mucolytic agents. Patients were also given additional treatments with antibiotics and bronchodilators, which might have influenced the overall outcome. Other limitations included the lack of airway clearance methods and potential suboptimal lung deposition of rhDNase. Nevertheless, the authors concluded that the use of rhDNase did not show a benefit in shortening length of hospital stay or duration of supplemental oxygen in hypoxemic infants with RSV bronchiolitis.¹⁴

The second study was also a randomized double-blind, placebo-controlled trial that evaluated the effect of rhDNase in shortening length of hospitalization and improvement in chest radiographs (CXR) in hospitalized infants with RSV.¹⁵ This study included 75 healthy full-term patients younger than 2 years of age with proven RSV. The outcomes assessed patients' improvement from admission to discharge through respiratory symptoms, CXR scoring system,

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

and length of stay. The chest X-ray scores had shown a significant improvement with rhDNase (0.46) while the score (0.60) was worsened in the placebo group ($p < 0.0001$). However, there was not any significant difference in length of stay and respiratory symptoms between the groups. Similar to the last study, it was unclear if the dose of medication or the route used allow for good deposition and clearance of the mucus. Even though there was a significant improvement in the CXR scores with rhDNase, there were not any significant differences in hospital length of stay and oxygen saturation between the two groups. Thus, these results challenge the clinical significance in the use of rhDNase for patients with RSV bronchiolitis.¹⁵

ASTHMA

The prevalence of asthma has increased at an annual rate of 1.4% from 2001 to 2010. In 2010, the prevalence of asthma in the United States was 8.4%, affecting 7 million children from the age of 0 to 17 years.¹⁶ The pathophysiological features of asthma include inflammation, edema of the bronchial mucosa, increased mucus production with airway plugging, and bronchospasms.¹⁷ Unlike bronchiolitis, patients with asthma have more benefits from the use of corticosteroids and β_2 -agonist. Patients with severe asthma exacerbation are also at a higher risk for complications such as atelectasis and increased airway obstruction.¹⁸ It is hypothesized that mucolytic agents such as rhDNase can help patients who have more severe asthma attacks.¹⁷

There is a limited amount of evidence with the use of mucolytic agents in pediatric patients with asthma. One randomized, double-blind, controlled clinical trial was performed to assess the efficacy of rhDNase in pediatric patients with asthma.¹⁹ Patients (N=121) in this study were previously on short acting beta agonist (~30%), steroids (38%), no medications (~25%), or combined steroids and short acting beta agonist (10%). They included patient with symptoms of acute asthma whose asthma score was ≥ 8 and who required at least two treatments with nebulized bronchodilators. Patients were given either a single

dose of nebulized 5mg rhDNase or 5mg sodium chloride following the second dose of bronchodilator. The primary objective was to assess the patients' asthma score (scale range 5-15) 1 hour and 24 hours after giving the study medication, and it was found to be insignificant ($p=0.23$ & $p=0.40$, respectively). Furthermore, the treatment did not prevent hospital admission. Overall, there was not any significant difference in time until discharge or duration of oxygen supplementation between the two groups. Majority of patients presented with mild disease, with only 4% of patients requiring admission to the ICU. Subgroup analysis of patients with asthma scores of at least 12 was performed; however, no significant improvement in asthma score was seen with the use of rhDNase in this group.¹⁹ Of note, another study done in patients 18-55 years old with acute asthma also did not show a difference in forced expiratory volume in 1 second (FEV_1), heart rate, and respiratory rate at any point post-randomization.²⁰ It is postulated that patients with more severe disease will have increased mucus plugging and hence more benefit from rhDNase treatment; however, this was not seen in this study. Due to the lack of evidence, it is concluded that nebulization with rhDNase given on arrival to the emergency department does not alleviate symptoms in children with moderate to severe acute asthma.¹⁹

ATELECTASIS IN MECHANICALLY-VENTILATED PATIENTS

Atelectasis can occur in patients on mechanical ventilation or with other severe respiratory infections.²¹ In addition, atelectasis and pneumonia are one of the common respiratory complications seen after surgery, especially cardiac surgery. Children on mechanical ventilation can develop atelectasis 10-54 percent of the time.²² These patients often have a greater risk of morbidity and increased length of stay. Common physiological features of atelectasis include impaired gas exchange, increased pulmonary vascular resistance, lung injury and excess amount of mucus secretions.²³ Potential treatment options include increasing ventilation parameters, regular

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

physiotherapy, position/proning, mucolytics, inhaled bronchodilators, and/or antibiotics. The treatment goal is to reduce recruitment of non-ventilated pulmonary segments and to prevent respiratory infections like pneumonia.²² Some data suggested that the use of dornase alfa may shorten the duration of mechanical ventilation, but it is not known if this regimen can effectively reverse atelectasis.²⁴

A single randomized placebo-controlled, double-blind study looked at 100 children (median age: 3 months) who had undergone cardiac surgery.²⁵ Dornase alfa was dosed depending on the patients' weight (<5kg: 0.2mg/kg or ≥5kg:0.1mg/kg twice a day). Even though there was not any significant difference in the incidence of reintubation ($p=1.0$) between the groups, there was a significant decrease by 24% in the overall ventilation time in the dornase alfa group ($p=0.043$). This study was powered for 80% with a sample size set at 220 patients, which was not reached and likely resulted in poor internal validity.²⁵ Dornase alfa has the potential benefit of decreasing time on ventilation post cardiac surgery, but it is not known if dornase alfa is effective at treating atelectasis in this patient population.

Three other studies attempted to determine if dornase alfa could help treat atelectasis.²⁶⁻²⁸ The first was a retrospective observational study performed in 46 patients (median age: 3.5 months) admitted to the pediatric intensive care unit with CXR evidence of atelectasis or infiltrates.²⁶ Three study groups were formed: patients with atelectasis, subgroup chosen to match for age and a diagnosis, and 17 cardiac surgery patients with atelectasis given no treatment. Patients were given rhDNase 0.1mg/kg intratracheally (via endotracheal tube) twice a day until extubation. Among 35 patients in group 1 who received rhDNase had a 76% significant improvement of atelectasis after 24 hours of treatment ($p=0.003$). The subgroup that was used to match with the historical data had a 100% improvement in atelectasis compared to 6% in the controlled group ($p=0.0007$). In addition, patients in the subgroup treated with dornase alfa had significant

improvement in ventilation parameters.²⁶ Limitation of this study included possible selection bias with the use of a matched subgroup to compare to the small number of controlled patients. This study utilized a different mode of administering the treatment drug by directly instilling the medication to the trachea. It is hypothesized that more lung deposition of drugs can be achieved with this mode compared to facemask nebulization.²⁹ In conclusion, this study showed that rhDNase is an effective adjunct to conservative therapy in children with atelectasis status post-cardiac surgery.

The next study was also a retrospective study looking at 38 patients (median age: 3.5 months) in the cardiac intensive care unit (CICU) who got ≤2 weeks of rhDNase while being mechanically ventilated.²⁷ The patients received 2.5mg of the rhDNase twice daily via nebulization if their atelectasis persisted for 2 days. The treatment was stopped once their atelectasis had improved. Patients were in the CICU for an average of 28.9 days. The outcomes of this study were to assess gas exchange and ventilator parameters before and 2 hours after each dose of rhDNase up to the fifth dose. There was a significant difference in the inspired oxygen (FiO_2) concentration from 0.45 pre-rhDNase compared to 0.40 post-rhDNase ($p\leq 0.001$). All other ventilator parameters (i.e. peak inspiratory pressure [PIP], positive end-expiratory pressure [PEEP], and partial pressure of arterial oxygen [PaO_2]) were not statistically significant. The patients' CXR atelectasis scores post rhDNase were significantly decreased compared to baseline (<5 doses: $p\leq 0.05$; 5-10 doses: $p\leq 0.01$, 10-15 doses: $p\leq 0.05$). However, no significant improvement was noted beyond 15 doses, indicating that short-term use of rhDNase may suffice. A subgroup analysis also demonstrated a significant improvement in the CXR atelectasis scores in patients who had greater than moderate amounts of polymorphonuclear neutrophils (PMN) or bacteria present in the pre-therapy trachea aspirate. It is unclear as to what is considered a moderate amount of PMN in this study. Nonetheless, this was the first study to show that atelectasis with bacteria or PMNs

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

had improved outcomes with the use of rhDNase, as well as showing that rhDNase might not be as effective beyond 15 doses.²⁷

Finally, the last study was a prospective review of 22 neonatal intensive care unit (NICU) patients (term=10; preterm=12) who were diagnosed with respiratory distress syndrome on mechanical ventilation.²⁸ These patients had previously tried conventional therapy for atelectasis without any adequate response. This study utilized nebulized rhDNase initially at a dose of 1mg/m² twice daily for three days. If the patients did not respond clinically after 3 days, they would receive a treatment of rhDNase that was instilled through the endotracheal tube at the same dose. Overall, these patients had significant improvements after three days of treatment in CXR scores, respiratory rate, FiO₂, and partial pressure of carbon dioxide (PCO₂) (p<0.001). Four patients relapsed and developed atelectasis following nebulized therapy, but their atelectasis improved after the endotracheal administration of rhDNase. This study allows us to formulate an idea of how to potentially treat critically-ill patients with atelectasis who have exhausted all other options by administering nebulized rhDNase and following with endotracheal administration if needed.²⁸

NEBULIZED HYPERTONIC SALINE VERSUS DORNASE ALFA

Nebulized hypertonic saline like dornase alfa has well-documented efficacy in patients with cystic fibrosis.³⁰ However, data on its efficacy for the treatment of atelectasis are only limited to newborns. Hypertonic saline primarily works by increasing hydration within the lungs to help liquefy the mucus, thus allowing for the dilution of mucus and increasing respiratory function regardless of DNA concentration within the mucus.³¹ There have been a few small randomized controlled trials that have shown the benefit of 3% hypertonic saline in patients with bronchiolitis by reducing the length of hospital stay and relieving symptoms in infants, and it is hypothesized that it may be beneficial in patients with atelectasis.³²⁻³⁴

An open label study evaluated the efficacy of hypertonic saline in 40 newborn (38 preterms; gestational age: 24-38 weeks and birth weight of 0.72 – 3.2 kg) with atelectasis.³⁵ They included patients with pulmonary atelectasis of ≥1 lobes. Patients also had to fail conventional therapy, which included frequent position, chest physiotherapy, aspiration, elective endotracheal suction, and medical treatment with N-acetylcysteine. Patients were given dornase alfa 1.25mg twice daily (2 hour dosing interval) for up to 3 days or 4 mL of 3% hypertonic saline every 2 hours for 3 doses, then every 4 hours for 5 doses, then every 6 hours until atelectasis disappeared. Both groups showed complete resolution of atelectasis, and the 3% hypertonic saline group had significantly improved CXR scores compared to rhDNase (p<0.001). Furthermore, significant improvement in oxygen saturation after treatment was observed with 3% hypertonic saline (98.4±1.4%) compared to rhDNase (97.1±2.1%;p<0.05). This was the only study that showed a beneficial effect in treating newborns with atelectasis with nebulized 3% hypertonic saline.³⁵

A randomized, prospective, double-blind, placebo-controlled trials was performed in adults comparing dornase alfa to hypertonic saline.³⁶ In this study, the researchers utilized 7% hypertonic saline instead of the 3% used in the previous study. The thought is that 7% saline may have higher mucolytic activity without the adverse effects of bronchospasm.³⁷ Thirty-three patients were included in this study and were divided into three groups: Group 1 received 4mL of nebulized normal saline; group 2 received 4mL of 7% hypertonic saline; and group 3 utilized 2.5mg of nebulized dornase alfa. All of the above regimens were administered twice daily. Patients were included if they were intubated and admitted to the intensive care unit with new onset lobar or multilobar lung atelectasis. Baseline CXR scores were compared at 34, 48 and 73 hours and also at 7 days. The results showed a decrease in CXR score from baseline to day 7 from 2.18±1.33 for rhDNase and 1.09±1.51 for 7% hypertonic saline compared to 1.00±1.79 for placebo (p=NS). No other differences were observed among

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

all three groups for PaO₂/FiO₂ levels and time to extubation.³⁶ The author concluded that there was not any improvement in atelectasis with the use of either rhDNase or hypertonic saline.³⁶ Even though this study was performed in adults, these results may be extrapolated to the pediatric population since there are not any pediatric studies comparing between 3% and 7% hypertonic saline for atelectasis.

Another retrospective study evaluating the cost-effectiveness and efficacy of nebulized rhDNase and hypertonic saline was performed in 87 newborns with unilateral or bilateral atelectasis who were on mechanical ventilation.³⁸ The patients were placed into four groups: control with no medication (group 1), 7% hypertonic saline (12h intervals between doses) twice daily which was dosed based on weight (<2.5kg=3mL & ≥2.5kg=4mL; group 2), rhDNase at 1.25mg (2h intervals between doses) twice daily (group 3) and combination therapy of 7% hypertonic saline and rhDNase twice daily (group 4) until resolution of atelectasis. A greater percent recovery of atelectasis was observed on day 3 with the combination therapy (27%, 70%, 81%, and 95% for placebo, 7% hypertonic saline, rhDNase, and combination therapy, respectively; p=NS). A significantly shorter duration of treatment with nebulizers was observed in group 2, group 3, and group 4 compared to group 1 (p<0.05).³⁸ A cost analysis was also performed on each treatment in the study. The additional cost per patient was US\$3.3 in group 2, approximately US\$75 in group 3 and US\$65 in group 4. The cost of one day of 7% hypertonic saline treatment was approximately US\$1, while the cost of daily rhDNase was approximately US\$26. The authors concluded that in newborns, monotherapy or combined treatment were effective and safe treatment options. The most efficient and cost effective of these methods is the co-administration of 7% hypertonic saline and rhDNase; though, the effect was not statistically different compared to other treatment groups.³⁸

CLINICAL APPLICATION

Infants with moderate to severe bronchiolitis and moderate to severe asthma exacerbation do not benefit clinically from the use of rhDNase based on the lack of solid clinical evidence. Thus, dornase alfa should not be initiated for these 2 clinical conditions without other complications. The benefits of rhDNase in infants with atelectasis while on mechanical ventilation has shown some relevant clinical outcomes. Even though these patients may benefit from the use of rhDNase, at present there is not any difference between the use of rhDNase and 3-7% hypertonic saline therapy. After reviewing the literature, it may be prudent to use a more cost-effective agent like nebulized hypertonic saline prior to initiating rhDNase.

Further research is needed to determine the appropriate dosing of this agent as well as the best mode of administration. Several studies have utilized different doses of dornase alfa without truly determining if these doses were effective at reducing the DNA concentrations within the patient's respiratory tract. Few studies utilized similar dosing to cystic fibrosis patients (i.e. 2.5mg/day), while other studies utilized higher doses of 5mg/day in anticipation of suboptimal lung deposition in young children with airway obstruction. Another study utilized dosing by instilling 0.1mg/kg intratracheally twice daily.³⁹ There have been a few case reports that describe the successful utilization of intratracheally administered rhDNase at fixed doses (i.e. 2.5-5mg/day either divided into q24h or q12h) or based on body surface area (i.e. 1-4mg/m²; the duration and frequency of this regimen vary among the case reports).^{29,39-41} However, there have not been any studies done thus far to assess improvement in outcomes for patients that utilized the intratracheal route of administration compared to those that utilized the nebulized formulations. More well-designed studies are needed to truly elucidate the most effective dose of rhDNase and route of administration to treat patient with mucus plugging. Figure 1 shows an algorithm on the potential use of dornase alfa in patients without cystic fibrosis based on the current clinical data.

A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

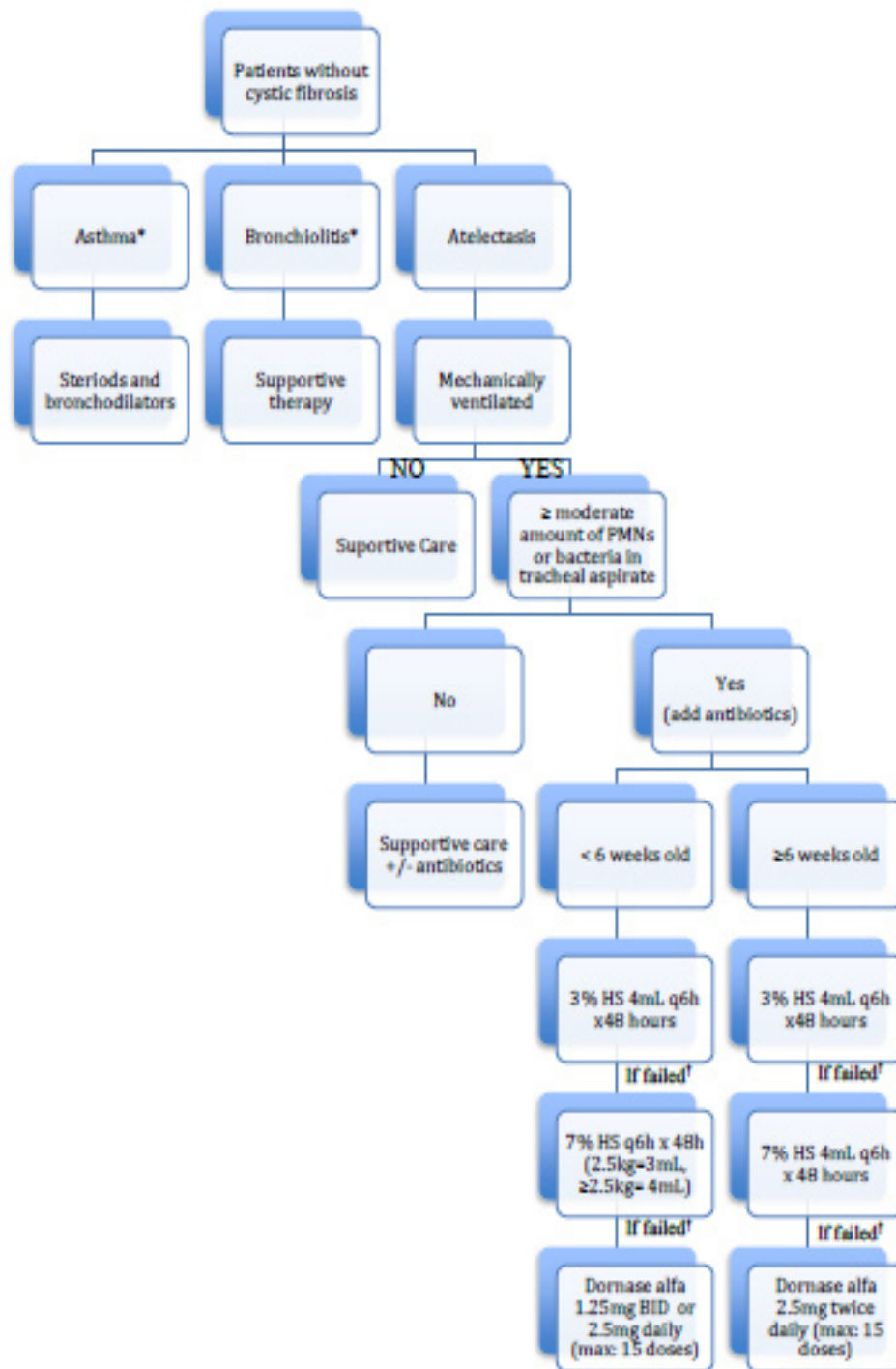


Figure 1. Proposed algorithm for the use of dornase alfa in pediatric patients without cystic fibrosis.^{14–15, 19, 27-28, 38}

*For patients with asthma and RSV bronchiolitis, dornase alfa was not shown to be clinically effective.

†Failure = worsening hypoxemia, failure of oxygenation index to improve to <15, or failure of atelectasis resolution on chest radiograph.

BID, twice daily; HS, hypertonic saline; PMN, polymorphonuclear neutrophils

CONCLUSIONS

The use of dornase alfa can be beneficial for patients whose underlying disorder is related to an increase in mucous production. Several clinical trials attempted to determine the effect of this treatment for specific indications other than cystic fibrosis; however, they were not able to show any significant differences in important clinical endpoints such as mortality and morbidity. Future larger randomized controlled trials should be performed to truly assess the cost effectiveness and efficacy of rhDNase in pediatric patients without cystic fibrosis. In the meantime, this regimen should only be used in patients with atelectasis who are on mechanical ventilation and who have exhausted other therapy like 3-7% hypertonic saline.

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A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

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A Literature Review on the use of Dornase Alfa in Pediatric Patients with Lower Respiratory Tract Illnesses other than Cystic Fibrosis

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