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Mini-symposium: Diagnosis and management of pulmonary lymphatic disorders

Rational use of mucoactive medications to treat pediatric airway disease

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Educational aims

The reader will be able to:

- Understand the classification of mucoactive medications based upon their proposed mechanism of action
- Identify medications that have been approved for secretion clearance therapy and their specific indications
- Appreciate how to evaluate the effectiveness of mucoactive medications for different airway diseases
- Recognize that medications that are effective for one disease may not be effective or may even be harmful for treating other diseases.

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ABSTRACT

Many airway diseases in children, notably bronchiolitis, cystic fibrosis (CF), non-CF bronchiectasis including primary ciliary dyskinesia, pneumonia, and severe asthma are associated with retention of airway secretions. Medications to improve secretions clearance, the mucoactive medications, are employed to treat these diseases with varying degrees of success. This manuscript reviews evidence for the use of these medications and future directions of study.

INTRODUCTION: DEFINITIONS AND TAXONOMY

Normal mucus is the lining fluid that protects the airway by entrapping and clearing inhaled particulate matter, and prevents fluid loss from the airway surface. Normal mucus is comprised of approximately 95% water, with polymeric mucins particularly MUC5B secreted from submucosal glands and MUC5AC secreted from mucous or goblet cells, providing the gel structure [1,2]. The mucous gel layer sits atop a periciliary layer of lower viscosity that contains attached mucins. The polymeric mucins form a gel through entanglement of long mucin chains. There is a relative paucity of cross-linking among discrete mucin polymers (Fig. 1 and Table 1).

During infection and inflammation, airway secretions also contain inflammatory and shed epithelial cells, particulates, microorganisms, secreted peptides and products of inflammation. This complex mix is called *phlegm* when it is in the airway and *sputum* when expectorated [3]. Mucoactive drugs are meant to improve the clearance as well as decrease the production of phlegm. In some disorders, as discussed later, airways are obstructed by atypical secretions, such as lymphatic leakage as in plastic bronchitis. In some diseases, notably CF, reduction in the height of the periciliary fluid layer and increased adhesivity of the mucous gel can lead to poor mucus clearance causing accumulation within the airway that eventually can become infected phlegm.

Mucoactive medications are defined by their presumed mechanism of action [4]. The term mucolytic, a medication that breaks down polymer bonds within the secretions, has sometimes been incorrectly used interchangeably with the term mucoactive medication. *Mucolytics* can be classic mucolytics that break down

Abbreviations: AAP, American Academy of Pediatrics; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane ion regulator; ENaC, epithelial sodium channel; ERK, extracellular regulating kinase; HS, hyperosmolar saline; NAC, N-acetyl L-cysteine; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; tPA, tissue plasminogen activator.

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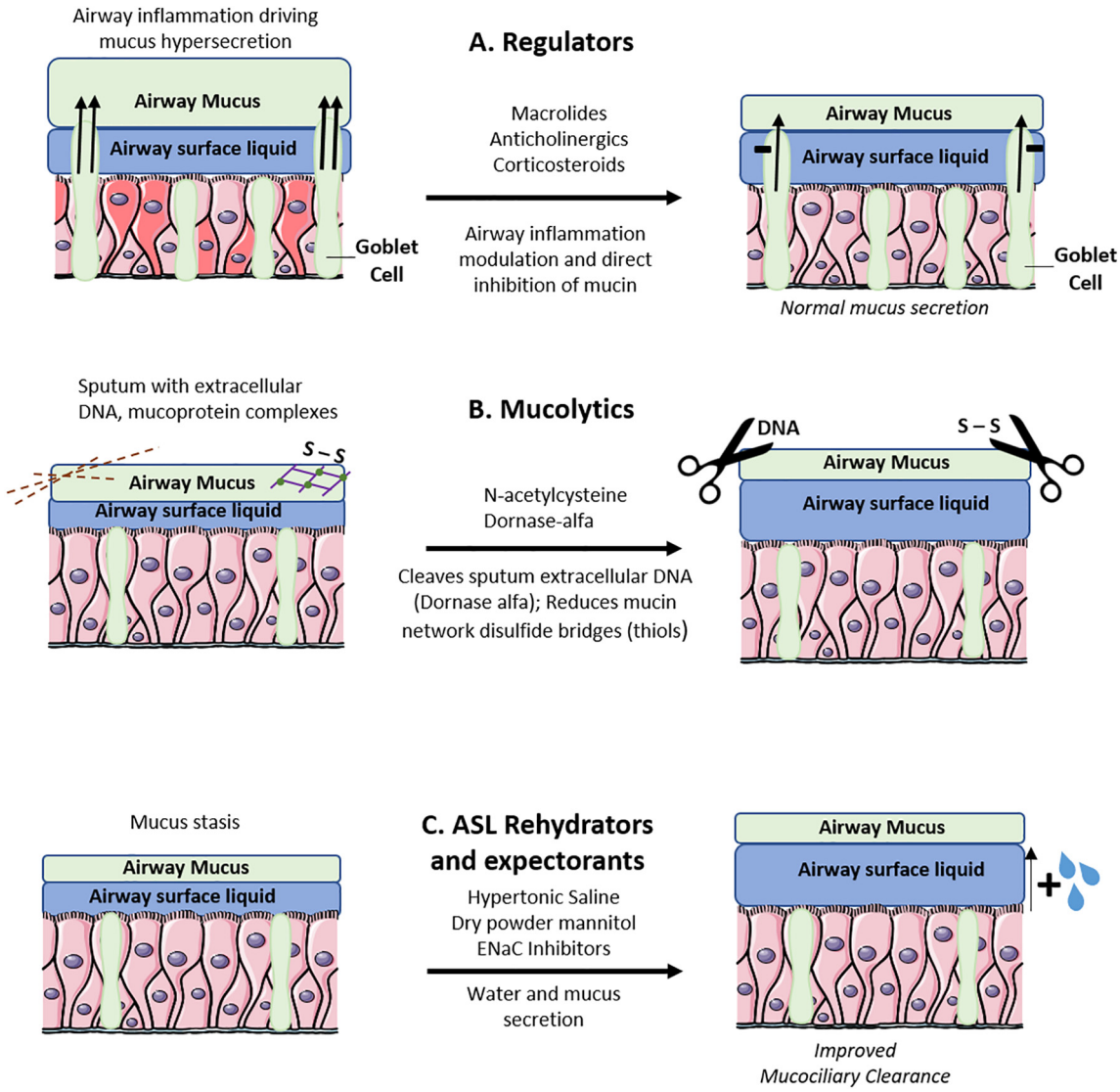

Fig. 1. (A) Regulators of goblet cell mucus secretion. Anticholinergics decrease mucus secretion by inhibition of neutrophil elastase driven mucin production (11). Anti-inflammatory agents such as corticosteroids and macrolides decrease mucus hypersecretion in airway inflammation. (B) Mucolytic agents break down mucus network structures to favorable biophysical properties for improved mucociliary clearance. Dornase-alfa hydrolyzes extracellular DNA in sputum and N-acetylcysteine reduces disulfide bonds in mucus networks. (C) Airway surface liquid (ASL) rehydrators reverse ASL height reduction to improve mucociliary clearance. These also increase mucus secretion as expectorators hypertonic saline and dry powder mannitol rehydrate ASL by hyperosmolar action. Epithelial sodium channel (ENaC) inhibitors prevent ASL depletion by hyperabsorption of sodium and water through ENaC.

Table 1
Mucus therapies in cystic fibrosis lung disease management.

Therapy	Mechanism	Form of Administration
Hypertonic Saline	Restoration of ASL Height	Aerosol mist
Mannitol	Restoration of ASL Height	Dry-power inhalation
ENaC Inhibitors	Restoration of ASL Height	N/A
Dornase alfa	DNA hydrolysis	Aerosol mist
N-acetylcysteine	Disulfide bond	Aerosol mist

mucins at the cross-linked disulfide bonds across adjacent cysteine residues. These classic mucolytics, of which N-acetyl L-cysteine (NAC) is the archetype, contain free sulfhydryl (thiol) groups that hydrolyze these disulfide bonds. Peptide mucolytics of which dornase alfa (Pulmozyme, Genentech, South San Francisco) is the archetype, depolymerize the secondary gel network comprised of polymeric DNA and filamentous (F-) actin. Because F-actin inhibits the effectiveness of dornase alfa, studies are underway evaluating the potential use of actin-protected dornase for more effective depolymerization of the DNA network (eg alidornase).

Expectorants are medications that increase the water content of secretions with the goal of improving clearance. One of the most widely studied of these is guaifenesin, but nearly all studies have shown guaifenesin and related compounds are no more effective than placebo [5]. Hyperosmolar medications such as hypertonic saline (HS) or dry powder mannitol are effective in increasing the hydration or fluid content of airway secretions and improving airway clearance in diseases such as CF and non-CF bronchiectasis [6,7].

Mucokinetic medications are intended to improve the effectiveness of ciliary propulsion or cough in secretion clearance. Although beta-agonists such as salbutamol increase ciliary beat frequency, there is little evidence that they are effective mucokinetic drugs [8]. It could also be argued that by inducing effective coughing, hyperosmolar medications also have mucokinetic properties. Inhaled surfactant decreases the adhesivity of airway secretions,

which potentially improves the effectiveness of ciliary and cough clearance [9].

Mucoregulatory medications decrease secretions by inhibiting mucus production or by decreasing inflammation. These medications include macrolide antibiotics that decrease mucin production by inhibiting the extracellular regulating kinase ERK1/2 [10], anticholinergic medications that may decrease mucus production by inhibiting neutrophil elastase driven mucin production [11], and corticosteroids which can decrease airway inflammation.

Mucospicic drugs (e.g. tetracycline) increase secretion viscosity. Secretions that are too thin might not be well cleared either by cough or by cilia, which is why mucus exists as a gel. Some patients, such as those with bronchorrhea, have extremely thin and liquid-like mucus. Mucospicic drugs may improve mucus clearance in these patients.

VIRAL BRONCHIOLITIS

Viral bronchiolitis is a clinical diagnosis in children characterized by obstructive dyspnea with increased respiratory effort, cough and - sometimes in young infants- apnea [12,13]. It is most frequently caused by respiratory syncytial virus (RSV), but other respiratory viruses such as human metapneumovirus, bocavirus, human rhinovirus, para-influenza virus, coronavirus, enterovirus can be implicated as well [12,13]. The pathobiology of bronchiolitis consists of edema of the small airways, increased local mucus production, and epithelial cell injury (necrosis and apoptosis) with ciliary dysfunction [14,15]. The sloughing of dead airway cells together with an influx of leukocytes contributes to the thick mucus plugs that obstruct the smaller airways. Due to their small airways, especially young infants are prone to airway obstruction and at increased risk for hospitalization [16–19]. Treatment for bronchiolitis is mainly supportive and as such there is need for an effective treatment targeting airway mucus obstruction.

The mucus plugs obstructing airways in viral bronchiolitis contain a large amount of polymerized, extracellular DNA [20]. As such, the use of the mucolytic dornase alfa, has been of interest [21,22]. Two randomized, placebo-controlled studies of nebulized dornase alfa in hospitalized children with mild to moderate bronchiolitis and a Cochrane review did not show a decrease in length of hospital stay or respiratory effort [20,23,24]. However, one study did show an improvement in chest radiograph defined atelectasis compared to placebo in young children with severe bronchiolitis [20]. Although chest X-ray abnormalities as a single finding are clinically less relevant, this finding is consistent with case series of mechanically ventilated children that reported radiological and clinical improvement after the use of dornase alfa [25]. A more prominent role for mucus plugging in the severe cases of bronchiolitis is suggested. For example: large amounts of neutrophils have been shown to be present in the airway of children who were mechanically ventilated or died from severe bronchiolitis [26–28] and excessive formation of neutrophil extracellular traps may contribute to increased DNA content in mucus, further increasing its viscoelasticity [29,30]. The current guideline from the American Academy of Pediatrics (AAP) on the treatment of bronchiolitis does not include a recommendation for using dornase alfa [31]. Future studies might focus on the use of dornase alfa in severe bronchiolitis and the possibilities for combined use with other aerosol agents to enhance small airway deposition.

The mucolytic NAC can be administered either by nebulization or orally, but has a low bioavailability as it undergoes first pass metabolism [32]. Although the use of NAC is carefully being explored for respiratory diseases in experimental settings, the clinical use of NAC for respiratory diseases is not recommended [33]. Despite one abstract reporting improvement of clinical severity scores when comparing nebulized NAC to salbutamol in children with viral bronchiolitis (full text article could not be retrieved), no studies have evaluated the role of NAC in viral bronchiolitis patients [34]. A possible beneficial effect for NAC can be hypothesized, as NAC functions as a free radical scavenger with antioxidative properties [35,36]. Oxidative stress is implicated in the pathophysiology of bronchiolitis. Laboratory studies showed increased levels of intracellular H_2O_2 in pulmonary epithelial cells after RSV infection [37] and the addition of NAC to RSV infected airway cultures reduces MUC5AC expression *in vitro* [37].

Nebulized HS decreases mucus plugging through the osmotic hydration of mucus, improving mucociliary clearance [38] and stimulates effective cough through an irritant effect. The use of 3% HS has been extensively studied in viral bronchiolitis. An in 2017 updated Cochrane review on a total of 4195 children, showed that the use of nebulized hypertonic saline compared to normal (0.9%) saline resulted in a slightly shorter length of hospitalization, but also reported low quality evidence [39,40]. Three randomized trials have been published since 2017. From them, only one study showed clinical improvement after three days of HS compared to one day of HS treatment but was underpowered [41], while two trials showed no beneficial effects for HS treatment compared to standard supportive care [42,43]. In most studies, HS was administered in combination with bronchodilator agents because of the fear for HS induced bronchospasms. But a retrospective cohort study focusing on the use of 3% HS without bronchodilators reported only one bronchospasm among 377 included children [44]. In severe bronchiolitis, one retrospective study including 104 children admitted to pediatric intensive care unit (PICU) for mechanical ventilation reported both a decreased duration of respiratory support and length of PICU stay in favor of HS [45]. Again, this might implicate a more prominent role for mucus obstruction in the pathobiology of viral bronchiolitis in children necessitating PICU admission. The AAP guideline on the treatment of bronchiolitis takes a neutral position on this topic and does not give recommendations on the use of HS in hospitalized children [31].

Although children suffering from bronchiolitis may present with wheezing in the acute phase, the respiratory distress originates from to small airway inflammation with extensive mucus plugging and (in most cases) not from bronchospasms. Randomized controlled trials show no significant benefits from nebulized albuterol for bronchiolitis and a Cochrane review from 2014 reported no benefits in terms of oxygen saturation or clinical scores [46]. A single study evaluating the effects of epinephrine, levalbuterol, and racemic albuterol/salbutamol in mechanically ventilated children with bronchiolitis found a statistically significant, but clinically futile effect on airway peak pressures [47]. As such, the AAP advises against the use of bronchodilators for viral bronchiolitis [31] and a recent clinical study reporting no negatively affected clinical outcome after decreased use of albuterol affirms this recommendation [48].

Surfactant (mucokinetic) is essential for normal small airway function and prevention of alveolar collapse. In health, surfactant decreases the adhesive interaction between the cilia and mucus. This enables effective mucociliary clearance as it allows the cilia to beat without becoming entangled in the airway mucus [49]. A decreased amount of airway phosphatidylcholine and impaired surfactant function in children suffering from bronchiolitis is reported [50,51]. This may be worse in severe cases of children who are in need of mechanical ventilation, as they suffer from more extensive airway inflammation [52]. A relationship between clinical recovery from bronchiolitis and improved surfactant activity is suggested [52]. To date, no clinical trials on the efficacy of exogenous surfactant administration in children hospitalized for mild to moderate bronchiolitis have been published. For children admitted to the PICU for bronchiolitis necessitating invasive venti-

lation, three randomized controlled trials have been published. A 2015 Cochrane review indicated favorable effect for duration of mechanical ventilation and PICU stay [52,53], but only included a low number of subjects. The current AAP guideline does not include a recommendation regarding the use of nebulized surfactant for bronchiolitis [31].

PLASTIC BRONCHITIS

Plastic bronchitis is a rare airway disorder defined by the presence of cohesive (rubbery) and branching casts that fill the airways [54]. This is different from mucus plugging where large, friable, non-branching phlegm contains mucin, inflammatory cells, and often bacteria. Although mucus plugs can be quite large, they do not have the extensive branching characteristics and rubbery texture of plastic bronchitis casts. They represent completely different etiologies. As one example, although extensive mucus plugging is common in patients with both CF and non-CF bronchiectasis, plastic bronchitis has never been reliably reported in patients with either of these disorders.

Plastic bronchitis is now identified as either being lymphatic or non-lymphatic in origin. The older classification systems that include inflammatory vs. non-inflammatory casts or Type 1 vs. Type 2 plastic bronchitis [55] were abandoned over 15 years ago when it was demonstrated that all forms of plastic bronchitis have some degree of inflammation. However, it is true that the non-lymphatic (or eosinophilic) plastic bronchitis has more inflammatory cells than classic or lymphatic plastic bronchitis [56].

Lymphatic plastic bronchitis appears to be the most common form of this disorder. It is most often reported in children and young adults with congenital heart disease, often after Fontan surgery and repair of single ventricle physiology. Plastic bronchitis is reported to occur in 3–4 % of these patients although the prevalence is probably under recognized [53]. As well described in another paper in this issue by Dr. Itkin and colleagues, there are characteristic abnormalities of the thoracic duct and lymphatic drainage that lead to plastic bronchitis when pulmonary vascular pressures are compromised.

Plastic bronchitis casts can be seen in some patients with sickle cell acute chest syndrome [57], primary lymphatic abnormalities, and following primary lymphatic malignancy. These lymphatic associated casts contain some cells, almost no fibrin, but extensive and congealed lymph. Because of this, classic mucolytics, peptide mucolytics, and fibrinolytic drugs are only partially effective in treating this disorder.

Eosinophilic plastic bronchitis produces branching casts that contain eosinophils and eosinophil degradation products including Charcot-Leyden crystals. Eosinophilic plastic bronchitis tends to occur in older children and young adults most of whom have a history of asthma and allergies [53]. These casts tend to occur in one branch of the airway and to reoccur only in that airway branch. Although this condition bears some resemblance to severe asthma where there is extensive mucus obstruction, even those patients have asthma tend to have relatively mild disease. In some respects, this disease is more like other eosinophilic diseases such as eosinophilic esophagitis.

It has been difficult to evaluate the effectiveness of mucoactive medications for the treatment of plastic bronchitis. There are relatively few subjects available for study in any one center leading to reports of individual case interventions. Also, the frequent confusion between plastic bronchitis and mucus plugging in those less familiar with these conditions makes it unclear which disorder has been treated.

Lymphatic plastic bronchitis does not respond to either classic or peptide mucolytics which should not be surprising as there appears to be little if any polymeric mucin or DNA in these casts. Tissue plasminogen activator (tPA) has been used acutely to degrade casts in patients with airway obstruction who are unable to tolerate bronchoscopy [58]. However, tPA should be considered a temporizing measure as it leads to extensive airway inflammation.

Tissue Factor activation has been associated with plastic bronchitis and so inhaled heparin has been used as chronic therapy to act both as an anti-inflammatory agent and to inhibit Tissue Factor. This therapy has met with variable success and appears to be most effective as a temporizing measure to prevent the formation of casts following bronchoscopic removal. There is no evidence for the effectiveness of inhaled hypertonic saline, NAC, steroids, salbutamol, or other medications for the treatment of lymphatic plastic bronchitis.

Eosinophilic or non-lymphatic plastic bronchitis often responds to corticosteroids administered in high dose or as pulse therapy. There is no proven effectiveness for the use of NAC, dornase alfa, hypertonic saline or other mucoactive medications for the treatment of non-lymphatic plastic bronchitis. Although it is possible that some of the newer biologics, particularly those that inhibit eosinophils, may be effective treatment of non-lymphatic plastic bronchitis, to our knowledge this has not been studied.

CYSTIC FIBROSIS AND NON-CYSTIC FIBROSIS BRONCHIECTASIS

A major feature of cystic fibrosis lung disease is mucus accumulation resulting in airway obstruction. Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane ion regulator (CFTR) protein gene, resulting in decreased chloride and bicarbonate secretion at the apical cell membrane of airway epithelial cells. This decreased anion secretion, coupled with CFTR-mediated increased sodium absorption via the epithelial sodium channel (ENaC), results in higher partial osmotic pressure and compression of the airway surface liquid height [59]. This reduction of the airway surface liquid height results in reduced ciliary beat frequency and thus impaired mucociliary clearance, in turn resulting in mucus plug formation and small airway obstruction [59]. These changes in the airway mucus clearance, together with the primary CFTR defect, result in repeated cycles of infection and inflammation, bronchiectasis, and progressive loss of lung function [60]. Ameliorating these CFTR dysfunction related changes to airway mucus is thus an important therapeutic strategy in CF.

The first class of therapeutics addressing abnormal airway mucus in CF is those that directly hydrate the mucus. Depletion of the airway surface liquid occurs through decreased CFTR-mediated fluid secretion with concomitant fluid absorption via the epithelial sodium channel (ENaC). Thus, one therapeutic strategy in CF lung disease is "rehydration" of the airway surface liquid by inhaling hyperosmolar agents. The premise of this class of therapies is that the airway surface liquid is pulled into the airway from the osmotic gradient generated [61]. The most widely used is aerosol hypertonic saline as a 7% sodium chloride solution [62]. Hypertonic saline, administered as an inhalation therapy twice daily, increases mucociliary clearance but not lung function in adults with CF [63]. In a double-blind, randomized control trial of inhaled hypertonic saline and isotonic saline in adults with CF, hypertonic saline failed to improve lung function but resulted in reduction of pulmonary exacerbations [64]. More recently, in the Saline Hypertonic in Preschoolers (SHIP) study, inhaled hypertonic saline was shown to improve the lung clearance Index, a marker of ventilation homogeneity, in children with CF aged 3–6 years [65]. Mannitol, which is a monosaccharide and is inhaled as a dry powder, has also been used in a similar fashion in CF and it improves lung function [66,67] and surface properties of CF sputum [68].

In non-CF bronchiectasis, the role of inhaled hyperosmolar therapy is less clear. Hypertonic saline failed to improvements in exacerbation rate, lung function, and quality of life when compared to inhaled isotonic saline in a 12-month clinical trial [69]. Similarly, dry powder mannitol failed show improvement in function or respiratory symptom assessment over placebo [70].

Another therapeutic strategy to rehydrate the airway surface liquid is targeting the epithelial sodium channel (ENaC). ENaC is an ion channel expressed on the apical surface of airway epithelial cells that conducts the resorption of sodium ions and water from the epithelial lumen into the epithelial cell [71]. In a CFTR deficient state there is evidence to suggest hyperabsorption of sodium and water via ENaC, which results in further depletion of the airway surface liquid [72]. There are ongoing efforts to develop ENaC inhibitors as potential therapeutics in CF to improve airway mucus and mucus clearance, though none are approved at the time of this review article.

CF airway mucus has abnormal viscoelastic properties [73] in part due to increased DNA and filamentous actin [74]. Another therapeutic strategy to improve airway mucus properties and enhance mucus clearance is to "thin" airway secretions with mucolytic and sputum-lytic agents. Dornase alfa has been widely adopted as an inhaled therapy in CF. Dornase alfa improves CF airway mucus properties by enzymatically degrading DNA, resulting in a decrease in mucus viscosity [21] and improvement in lung function [75]. While dornase alfa has been shown to be clinically beneficial in CF lung disease, it has been shown to be harmful in non-CF bronchiectasis, with increased risk of exacerbations and decrease in lung function when compared to placebo [76]. Another proposed mucolytic therapy in CF is N-acetylcysteine, which disrupts the mucus architecture through hydrolysis of the disulfide bonds tethering mucus strands. However, there are no studies to date to show clinical benefit in CF lung disease [77].

ASTHMA

Asthma is a common, chronic inflammatory disorder of the airways that is primarily associated with bronchial hyperresponsiveness and intermittent airflow obstruction. Mucus hypersecretion and airway obstruction by mucus plugs often contribute to disease symptoms, in particular during exacerbations and especially with severe, life-threatening or fatal asthma attacks [78–80]. Current, well-established, asthma medications, including both controller and reliever therapies such as β2-agonists [81–83], anticholinergics [32,84–86], and corticosteroids [87] have putative mucoregulatory activities. However, in the clinical evaluation of these agents, any direct mucoregulatory effects (e.g. reduction of mucus secretion or occurrence of mucus plugs) will be difficult to distinguish from their other more primary bronchodilator and/or immunomodulatory functions. On the other hand, macrolides, have been shown to decrease mucus secretion both *in vitro* and *in vivo* [88], and may have a role as an anti-inflammatory to treat asthma, but their clinical benefit in both children and adults with chronic asthma has not been established [89].

Mucolytic agents, including dornase alfa and NAC, are not used in the management of asthma. There is no evidence of a clinical benefit of dornase alfa in children [90] or adults [91] with moderate to severe asthma. Nevertheless, some clinicians appear to use dornase alfa in mechanically ventilated children,[92] fueled by case reports showing improvement agent [93,94]. The administration of NAC in asthma has met with very limited success, as more recently assessed in a systematic review and meta-analysis.[95] Although expectorants, such as hypertonic saline, which is frequently used for sputum induction during bronchial challenge, have been shown to improve mucociliary and cough clearance in asthmatics in small studies, [96,97] these agents are currently not recommended in asthma management and indeed are known to induce mucus secretion and bronchospasm.

Although these findings reduce the likelihood that mucoactive agents in current use will play a role in the pharmacological approach to (pediatric) asthma, increasing insight into asthma endotypes (e.g. allergic, non-allergic, neutrophilic, cough-dominant etc), in which different immune cells (e.g. eosinophils vs neutrophils) function as the primary drivers of asthma pathophysiology, may establish the relative importance of mucus in defining clinical signs of illness, particularly in T17 dominant (non-eosinophilic) asthma. As such, the concept of secretory hyperresponsiveness, which has strong links to IL-13 and neutrophil elastase mediated responses, [11,98,99] may serve as an anchor point for the use of mucoactive agents in asthma.

PEDIATRIC CRITICAL CARE: MECHANICALLY VENTILATED CHILDREN

Children with acute respiratory failure undergoing invasive mechanical ventilation in the pediatric intensive care unit (PICU) comprise a patient group highly vulnerable for airway obstruction by phlegm. Airway obstruction in these children increases the risk of atelectasis, ventilator-associated pneumonia and need for high peak airway pressures. At the same time, an indwelling endotracheal tube provides an opportunity for new local drug delivery for mucoactive agents [100,101].

Disappointingly, few randomized controlled studies have so far studied the effectiveness of mucoactive agents during invasive mechanical ventilation in an either specific or general PICU population. McKinley et al. have investigated the effect of no saline versus 0.225% or 0.9% saline installation before routine endotracheal suction to remove phlegm in 427 children receiving ventilator support [102]. However, in this non-blinded trial, no statistically significant differences in duration of mechanical ventilation, oxygen therapy or PICU stay between the groups were found. Similarly, Shein et al. have focused on expectorants by studying routine nebulization with hypertonic (3%) saline versus normal (0.9%) saline in a pilot study [103]. With a very small sample size ($n = 18$), they found no differences between the groups for a number of outcomes, including duration of mechanical ventilation or chest X-ray atelectasis score, as well as respiratory mechanics parameters before and after intervention. Finally, Riethmueller and coworkers studied the mucolytic agent aldornasfa versus normal saline in 88 mechanically ventilated children with an age of 0–2 years after cardiac surgery [104]. Nebulization with dornase alfa resulted in a statistically significant reduction in duration of ventilator support by approximately one day, as well as a trend ($p = 0.051$) towards improved chest X-ray atelectasis scores. However, the primary endpoint of this study, re-intubation incidence, was not significantly different between the groups.

These results do not make any recommendations on routine mucoactive medication strategies for PICU patients possible. They merely reveal the need for further randomized trials in this field. With this, we need to realize that subgroups of PICU patients either with or without active respiratory inflammation and infection may react differently to expectorants versus pure mucolytics. As such, better insight into the dynamics of mucus and phlegm viscoelastic properties and contents (e.g. extracellular DNA, proteins) during the course of mechanical ventilation for pediatric critical illnesses is highly relevant.

CONCLUSION & FUTURE RESEARCH DIRECTIONS

A characteristic of many airway diseases is secretion retention. Although various mucoactive medications, with diverse mechanisms of action, have been studied as potential therapies, there are few well controlled clinical studies supporting their use; especially for older medications. There has been a renewed interest in testing existing drugs and developing new medications targeting specific abnormalities in mucus clearance. This is driven, in large part, by a better understanding of the importance of secretion clearance and the mechanism(s) of action of mucoactive medications as well as a better understanding of how mucus secretion and clearance changes with disease type and disease activity.

AUTHOR CONTRIBUTIONS

Linssen, RSN: contributed to the writing of the manuscript.
Ma, J: contributed to the writing of the manuscript.
Bem, RA: contributed to the writing of the manuscript.
Rubin, BK: contributed to the design of the study, contributed to the writing of the manuscript.

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