

# Mucolytics, Expectorants, and Mucokinetic Medications

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- Introduction
- Expectorants
- Mucolytics
  - Classic Mucolytics
  - Peptide Mucolytics
  - Nondestructive Mucolytics
- Mucokinetic Agents
- Abhesives/Lubricants
- Summary

**In health, the airways are lined by a layer of protective mucus gel that sits atop a watery periciliary fluid. Mucus is an adhesive, viscoelastic gel, the biophysical properties of which are largely determined by entanglements of long polymeric gel-forming mucins, MUC5AC and MUC5B. This layer entraps and clears bacteria and inhibits bacterial growth and biofilm formation. It also protects the airway from inhaled irritants and from fluid loss. In diseases such as cystic fibrosis there is almost no mucin (and thus no mucus) in the airway; secretions consist of inflammatory-cell derived DNA and filamentous actin polymers, which is similar to pus. Retention of this airway pus leads to ongoing inflammation and airway damage. Mucoactive medications include expectorants, mucolytics, and mucokinetic drugs. Expectorants are meant to increase the volume of airway water or secretion in order to increase the effectiveness of cough. Although expectorants, such as guaifenesin (eg, Robatussin or Mucinex), are sold over the counter, there is no evidence that they are effective for the therapy of any form of lung disease, and when administered in combination with a cough suppressant such as dextromethorphan (the “DM” in some medication names) there is a potential risk of increased airway obstruction. Hyperosmolar saline and mannitol powder are now being used as expectorants in cystic fibrosis. Mucolytics that depolymerize mucin, such as N-acetylcysteine, have no proven benefit and carry a risk of epithelial damage when administered via aerosol. DNA-active medications such as dornase alfa (Pulmozyme) and potentially actin-depolymerizing drugs such as thymosin  $\beta_4$  may be of value in helping to break down airway pus. Mucokinetic agents can increase the effectiveness of cough, either by increasing expiratory cough airflow or by unsticking highly adhesive secretions from the airway walls. Aerosol surfactant is one of the most promising of this class of medications. *Key words: mucus, mucin, cystic fibrosis, airway secretions, expectorant, mucolytic, mucokinetic, mannitol, N-acetylcysteine, dornase alfa, thymosin, surfactant.* [Respir Care 2007;52(7):859–865. © 2007 Daedalus Enterprises]**

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## Introduction

The airway mucosa responds to infection and inflammation in a variety of ways. This response often includes surface mucous (goblet) cell and submucosal gland hyperplasia and hypertrophy, with mucus hypersecretion. Products of inflammation, including neutrophil-derived deoxyribonucleic acid (DNA) and filamentous actin (F-actin), effete cells, bacteria, and cell debris all contribute to mucus purulence. Expectoated mucus is called sputum. Mucus is usually cleared by ciliary movement, and sputum is cleared by cough.<sup>1</sup>

The general term for medications that are meant to affect mucus properties and promote secretion clearance is "mucoactive." These include expectorants, mucolytics, mucoregulatory, mucospissic, and mucokinetic drugs.<sup>2</sup> Mucoactive medications are intended either to increase the ability to expectorate sputum or to decrease mucus hypersecretion. This paper primarily addresses mucolytic and mucokinetic medications, but will also cover the expectorants because of recent interest and developments (Table 1). Mucoregulatory medications such as anticholinergics will not be discussed.

## Expectorants

Expectorants are defined as medications that improve the ability to expectorate purulent secretions. This term is now taken to mean medications that increase airway water or the volume of airway secretions, including secretagogues that are meant to increase the hydration of luminal secretions (eg, hypertonic saline or mannitol) and adhesives that decrease the adhesivity of secretions and thus unstick them from the airway (eg, surfactants). Expectorants do not alter ciliary beat frequency or mucociliary clearance. Oral expectorants were once thought to increase airway mucus secretion by acting on the gastric mucosa to stimulate the vagus nerve, but that is probably inaccurate. The most commonly used expectorants are simple hydration, including bland aerosol, oral hydration, iodide-containing compounds such as super-saturated potassium iodide or iodinated glycerol, glyceryl guaiacolate (guaifenesin), and the more recently developed ion-channel modifiers such as the P2Y2 purinergic agonists.

Dehydration might increase the tenacity of secretions by increasing adhesivity. The more secretions adhere to the epithelium, the more difficult they are to cough up.<sup>3</sup> If there was an effective way to rehydrate the surface of dry secretions, this would be of benefit. Most of these medications and maneuvers are ineffective at adding water to the airway, and those that are effective are also mucus secretagogues that increase the volume of both mucus and water in the airways.

Table 1. Mucoactive Agents

Mucoactive Agent	Potential Mechanisms of Action
Expectorants	
Hypertonic (7%) saline	Increases secretion volume and perhaps hydration
Dry powder mannitol	Increases mucus secretion
Guaifenesin	Not shown to be effective
Classical mucolytics	
N-acetylcysteine	Severs disulfide bonds that link mucin oligomers. Anti-oxidant and anti-inflammatory
Nacystelyn	Increases chloride secretion and severs disulfide bonds
Peptide mucolytics	
Dornase alfa	Hydrolyzes DNA polymer and reduces DNA length
Thymosin $\beta_4$	Depolymerizes filamentous actin
Nondestructive Mucolytics	
Heparin	May break both hydrogen and ionic bonds
Cough clearance promoters	
Bronchodilators	Can improve cough clearance by increasing expiratory flow
Surfactants	Decreases sputum adhesiveness

DNA = deoxyribonucleic acid

Moderate hydration in patients with chronic bronchitis does not significantly affect sputum volume or ease of expectoration.<sup>4</sup> Systemic over-hydration can lead to mucosal edema and impaired mucociliary clearance.<sup>5</sup>

Despite widespread use, iodinated compounds, guaifenesin, and simple hydration are ineffective as expectorants.<sup>6</sup> Iodide-containing agents (eg, super-saturated potassium iodide [commonly known as SSKI]) are generally considered to be expectorants thought to stimulate the secretion of airway fluid. Iodopropylidene glycerol may briefly increase tracheobronchial clearance, as measured with radiolabeled aerosol in patients with chronic bronchitis.<sup>7</sup> However, in a double-blinded crossover study in subjects with stable chronic bronchitis, iodopropylidene glycerol did not significantly change pulmonary function, gas trapping, or sputum properties.<sup>8</sup>

Guaifenesin (sold as cough medications such as Robatussin and Mucinex) is usually considered an expectorant rather than a mucolytic. It can be ciliotoxic when applied directly to the respiratory epithelium.<sup>9</sup> Although it may stimulate the cholinergic pathway and increase mucus secretion from the airway submucosal glands, neither guaifenesin nor glycerol guaiacolate has been clinically effective in randomized controlled trials. Because expectorants are meant to increase the volume of airway secretions (presumably to improve the effectiveness of cough), it is astounding that these would ever be sold in combination

with a medication meant to suppress cough, such as dextromethorphan (the “DM” in some medication names). If these combinations were actually effective, the patient’s airway would rapidly fill up with secretions while their ability to cough these secretions out of the airway was suppressed!

Agents that increase transport across ion channels, such as the cystic fibrosis transmembrane regulator (CFTR) chloride channel or the calcium-dependent chloride channel, and agents that increase water transport across the airway aquaporin water channels may increase the hydration of the periciliary fluid and thus aid expectoration. Chloride conductance through the  $\text{Ca}^{2+}$ -dependent chloride channels is preserved in the CF airway. The tricyclic nucleotides, uridine triphosphate and adenosine triphosphate, regulate ion transport through P2Y2 purinergic receptors that increase intracellular calcium. Uridine triphosphate aerosol, alone or in combination with amiloride, increases trans-epithelial potential difference and the clearance of inhaled radioaerosol.<sup>10</sup> There is active development of novel P2Y2 purinergic receptor agonists for clinical use.<sup>11,12</sup>

For many years, sputum induction with hyperosmolar saline inhalation has been used to obtain specimens for the diagnosis of pneumonia. Similarly, powdered mannitol improves quality of life and pulmonary function in adults subjects with non-CF bronchiectasis, and significantly improves the surface adhesivity and cough clearability of expectorated sputum.<sup>13</sup> Subsequent studies confirmed that long-term use of inhaled hyperosmolar saline improves pulmonary function in patients with CF,<sup>14,15</sup> and inhaled mannitol is beneficial in non-CF bronchiectasis.<sup>16</sup> Although this therapy is readily available and inexpensive, it has been reported that hypertonic saline aerosol is not as effective as dornase alfa in the therapy of CF lung disease.<sup>17</sup> Furthermore, hypertonic saline has an unpleasant taste and induces coughing, which may limit its acceptance and thus its efficacy as a long-term therapy.

Sodium bicarbonate (2%) is a base that has occasionally been used for direct tracheal irrigation or as an aerosol. By increasing the local bronchial pH, sodium bicarbonate weakens the bonds between the side chains of the mucus molecule, which decreases mucus viscosity and elasticity. Local bronchial irritation may occur with a bronchial pH of greater than 8.0. Sodium bicarbonate has not been clinically demonstrated to improve airway mucus clearance. There is little to recommend its use.

The principal polymer component of normal airway mucus is the gel-forming mucin glycoproteins. Mucin protein is decorated with oligosaccharide side chains, and the elongated glycoproteins linearly polymerize to form a tangled network secondary structure. In sputum, a secondary polymer network is composed of neutrophil-derived DNA and cell-wall-associated filamentous actin (F-actin).<sup>18</sup> This secondary polymer network is responsible for many of the

abnormal properties of purulent secretions and, at least in the CF airway, there is very little mucin present at all (Fig. 1).<sup>19</sup>

Mucus is a gel, and both its viscous (energy loss) and elastic (energy storage) properties are essential for mucus spreading and clearance.<sup>20</sup> Mucociliary clearance depends on an optimal ratio of viscosity to elasticity.<sup>21</sup>

## Mucolytics

Mucolytics are medications that change the biophysical properties of secretions by degrading the mucin polymers, DNA, fibrin, or F-actin in airway secretions, generally decreasing viscosity. This will not necessarily improve secretion clearance, because sputum that is more viscous but less sticky tends to clear better with cough.<sup>2,22</sup> Although this may seem counterintuitive at first, consider a peashooter to be a reasonable model for a proximal, cartilaginous, conducting airway, and the pea inside is an obstructing mucus plug. Shooting that pea out depends on how hard you blow (cough velocity and flow) and how much it sticks to the side of the shooter (adhesion). These being equal, it is far easier to shoot that pea out than to clear out a similar volume of pea soup in the shooter. In this case, pea soup is equivalent to sputum that has been thinned by a mucolytic.

### Classic Mucolytics

Classic mucolytics depolymerize the mucin glycoprotein oligomers by hydrolyzing the disulfide bonds that link the mucin monomers. This is usually accomplished by free thiol (sulfhydryl) groups, which hydrolyze disulfide bonds attached to cysteine residues of the protein core. The best known of these agents is N-acetyl L-cysteine (NAC). No data convincingly demonstrate that any classic mucolytic, including NAC, improves the ability to expectorate mucus. Acetylcysteine can decrease mucus viscosity *in vitro*,<sup>23</sup> but, because oral acetylcysteine is rapidly inactivated and does not appear in airway secretions, it is ineffective *in vivo*. Published evidence suggests that oral acetylcysteine may improve pulmonary function in selected patients with chronic suppurative lung disease, including chronic obstructive pulmonary disease (COPD),<sup>24,25</sup> but the clinical benefit observed is probably due to antioxidant properties. Daily use of acetylcysteine reduces the risk of re-hospitalization for COPD exacerbation by approximately 30%,<sup>26</sup> but it does not modify the outcomes of COPD exacerbations.<sup>27</sup> However a well-controlled, large, long-term study of daily NAC at fairly high dose had no effect on pulmonary function, quality of life, exacerbation rate, or hospitalization rate in persons with moderately severe COPD (stage 3 or 4 in the COPD staging system of the Global

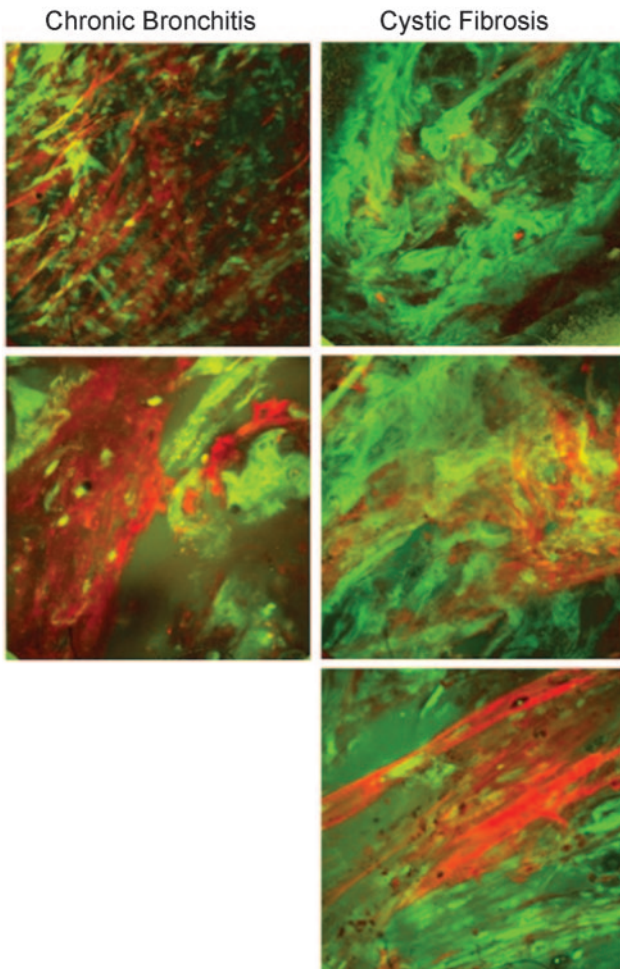


Fig. 1. Laser scanning confocal micrograph showing the mucin polymers (Texas red-conjugated *Ulex europaeus* agglutinin (UEA) lectin) and deoxyribonucleic acid (DNA) polymers (green YoYo-1) in bronchitis and cystic fibrosis (CF) sputum. Sputum was collected at the start of a pulmonary exacerbation of bronchitis or CF. Note more green-stained DNA polymers and fewer red-stained mucin polymers in the CF sputum than in the chronic bronchitis sputum. The punctate YoYo-1 staining of the chronic bronchitis sputum suggests that there was more DNA in intact inflammatory cell nuclei. There was 45% less mucin and 416% more DNA by area in CF sputum than in chronic bronchitis sputum. (From Reference 19, with permission.)

Initiative for Chronic Obstructive Lung Disease or GOLD guidelines).<sup>28</sup>

The regular use of aerosol NAC may be harmful in persons with CF, producing unacceptable adverse effects and an indication of decreased pulmonary function in some patients.<sup>29</sup> This may be due, in part, to NAC selectively depolymerizing the essential mucin polymer structure and leaving the pathologic polymers of DNA and F-actin intact. However, a recent pilot clinical study suggested that high-dose oral NAC may effectively decrease the hyper-inflammatory airway state characteristic of CF.<sup>30</sup> Because there are no data that show aerosol NAC to be effective for

lung disease, and because of the high prevalence of adverse effects, its use is not recommended. It is theoretically possible that NAC aerosol can increase the risk of airway infection and inflammation by disrupting the protective mucin layer.

There are several similar compounds that contain sulfhydryl groups that can effectively depolymerize mucin polymers in vitro. Although many of these are better tolerated than NAC, none have been clearly demonstrated effective in improving mucus clearance.

### Peptide Mucolytics

The mucin polymer network is essential for normal mucus clearance. It may be that the classic mucolytics are generally ineffective because they depolymerize essential components of the mucus gel. With airway inflammation and inflammatory cell necrosis, a secondary polymer network of DNA and F-actin develops in purulent secretions. In contrast to the mucin network, this pathologic polymer gel serves no obvious purpose in airway protection or mucus clearance. In patients with stable CF there is almost no mucin in airway secretions,<sup>19</sup> and although mucin can be secreted in response to an exacerbation of disease, there is still much less mucin than DNA in the CF airway.<sup>31</sup>

The peptide mucolytics are designed specifically to depolymerize the DNA polymer (dornase alfa) or the F-actin network (eg, gelsolin, thymosin  $\beta_4$ ) and are most effective when sputum is rich in DNA pus. The only peptide mucolytic agent approved for use in the United States is dornase alfa (Pulmozyme) for the treatment of CF lung disease.<sup>32,33</sup> Aerosolized dornase alfa reduces the viscosity and adhesiveness of infected sputum in vitro<sup>34</sup> and modestly improves FEV<sub>1</sub> in patients with CF.<sup>33,35,36</sup> For reasons that are not clear, dornase alfa is not uniformly effective for the treatment of CF airway disease, and efficacy does not seem to be related to sputum DNA content. Limited and anecdotal data suggest that dornase alfa may be effective in treating *some* persons with non-CF bronchiectasis, including some patients with primary ciliary dyskinesia.<sup>37</sup>

A beneficial in vitro effect on rheological and transport properties has been reported in the purulent sputum of chronic bronchitis.<sup>38</sup> However, in patients with chronic bronchitis, dornase alfa does not appear to improve pulmonary function or reduce morbidity.<sup>37</sup> Although dornase alfa was not effective in severe chronic bronchitis, there have been no published studies of its efficacy in patients with milder disease.

Actin is the most prevalent cellular protein in the body; it plays a vital role in maintaining the structural integrity of cells. Under proper conditions, actin polymerizes to form F-actin. Extracellular F-actin probably contributes to the viscoelasticity of expectorated CF sputum, although

this has not been definitively demonstrated.<sup>18,39</sup> In vitro studies suggest that F-actin depolymerizing agents used in conjunction with dornase alfa may reduce sputum viscoelasticity and cohesivity more than either used alone.<sup>40</sup>

### Nondestructive Mucolytics

Mucin is a polyionic tangled network, and the charged nature of the oligosaccharide side chains helps to hold this network together as a gel. Several agents have been proposed that can “loosen” this network by charge shielding. These agents include low-molecular-weight dextran, heparin, and other sugars or glycoproteins.<sup>41</sup> To date there have been no reported clinical studies of these drugs for the therapy of airway disease.

### Mucokinetic Agents

A mucokinetic medication is a drug that increases mucociliary clearance, generally by acting on the cilia. Although a variety of medications, such as tricyclic nucleotides,  $\beta$ -agonist bronchodilators, and methylxanthine bronchodilators, all increase ciliary beat frequency, these agents have only a minimal effect on mucociliary clearance in patients with lung disease.<sup>42</sup> The reason for this is probably a combination of factors, including the limited potential for efficacy in an airway with dysfunctional cilia or denuded of cilia. Most of these agents are also mucus secretagogues that may paradoxically increase the burden of airway secretions. Bronchodilator medications can also increase airway collapse in patients with bronchomalacia, because they relax airway smooth muscle.<sup>43</sup> Therefore, the only persons for whom these medications are recommended are those who have improvement in expiratory airflow following their use. Because increased expiratory airflow can enhance the effectiveness of cough,<sup>44</sup> bronchodilators might be better considered cough clearance promoters.

### Abhesives/Lubricants

Surfactant can reduce sputum adhesivity and increase the efficiency of energy transfer from the cilia to the mucus layer. Several investigators have observed a decrease in the amount of bronchial surfactant<sup>45</sup> and abnormal sputum phospholipid composition<sup>46,47</sup> in patients with chronic bronchitis. Furthermore, acute and chronic airway inflammation leads to the production of secretory phospholipase A2, as a product of arachidonic acid metabolism. Airway secretory phospholipase A2 can break down surfactant phospholipids into non-surface-active lysophospholipids,<sup>48</sup> it is a potent mucin secretagogue, and it can produce secretory hyperresponsiveness to other inflammatory stimuli and thus exacerbate airway obstruction.<sup>49</sup>

Table 2. Mucoactive Drugs in Development

Surfactant
Thymosin $\beta_4$
Dry powder mannitol
Denufosal tetrasodium (INS37217 respiratory) for cystic fibrosis
Erdosteine
Heparin

Sputum tenacity, which is the product of adhesivity and cohesivity, has the greatest influence on the cough clearability of sputum.<sup>3</sup> Decreasing tenacity with surfactant effectively increases the cough transportability of secretions.<sup>47</sup> We found that 14 days of aerosolized surfactant increased in vitro sputum transportability, improved FEV<sub>1</sub> and FVC by more than 10%, and significantly decreased trapped thoracic gas (as measured by the ratio of residual volume to total lung capacity) in patients with stable chronic bronchitis. This effect persisted for at least a week after treatment was completed.<sup>50</sup>

Ambroxol has been thought to stimulate surfactant secretion, and has been used for many years in Europe for the management of chronic bronchitis, but it has never been approved in the United States or Canada. The results of clinical studies of ambroxol are conflicted; some found clinical benefit,<sup>51,52</sup> whereas others found no benefit.<sup>53</sup>

Some of the expectorant activity of the classic mucolytics may be attributed to abhesive action. Although decreasing the viscosity of a mucus plug might actually reduce sputum cough clearability by decreasing the height of the mucus layer, if a mucolytic decreases mechanical impedance at the epithelial surface (ie, frictional adhesive forces), it is possible to “unstick” secretions from the underlying ciliated epithelium, which would make airflow-dependent clearance more efficient.

### Summary

Airway mucus hypersecretion and mucus retention is an important problem for patients with chronic airway disease. The burden of asthma, chronic bronchitis, bronchiectasis, CF, and other airway diseases poses one of the most important public health problems internationally. Medications that improve mucus clearance would provide relief to millions of persons around the world. Although many medications have been used clinically as mucoactive therapy, the data only support a handful of these medications. This is a topic of ongoing investigation and rapid change (Table 2).

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