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Secretory Hyperresponsiveness and Pulmonary Mucus Hypersecretion

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The term bronchial hyperresponsiveness is generally used to describe a heightened airway smooth muscle bronchoconstrictor response measured by bronchoprovocation testing. However, the airway also responds to inflammation or bronchoprovocation with increased mucus secretion. We use the term "secretory hyperresponsiveness" to mean increased mucus secretion either intrinsically or in response to bronchoprovocation. This is not the same as retained phlegm or sputum. Unlike smooth muscle contraction, which is rapidly reversible using a bronchodilator, mucus hypersecretion produces airflow limitation that reverses more slowly and depends upon secretion clearance from the airway. Certain groups of patients appear to have greater mucus secretory response, including those with middle lobe syndrome, cough-dominant ("cough-variant") asthma, and severe asthma. Secretory hyperresponsiveness also is a component of forms of lung cancer associated with bronchorrhea. An extreme form of secretory hyperresponsiveness may lead to plastic bronchitis, a disease characterized by rigid branching mucus casts that obstruct the airway. Secretory hyperresponsiveness and mucus hypersecretion appear to be related to activation of the extracellular-regulated kinase 1/2, signaling through the epidermal growth factor receptor, or secretory phospholipases A2. Recognizing secretory hyperresponsiveness as a distinct clinical entity may lead to more effective and targeted therapy for these diseases. CHEST 2014; 146(2):496-507

ABBREVIATIONS: BAC = bronchoalveolar carcinoma; BHR = bronchial hyperresponsiveness; CDA = cough-dominant asthma; CF = cystic fibrosis; EGFR = epidermal growth factor receptor; ERK = extracellular-regulated kinase; LPS = lipopolysaccharide; MEC = mucoepidermoid carcinoma; MLS = middle lobe syndrome; OPEP = oscillatory positive expiratory pressure; PB = plastic bronchitis; PBB = protracted bacterial bronchitis; ROS = reactive oxygen species; TKI = tyrosine kinase inhibitor; TNF = tumor necrosis factor; tPA = tissue plasminogen activator

In animal studies, exposure to secretory phospholipases A2 can make the airway hyperresponsive to secretagogues such as neutrophil elastase or bacterial endotoxin (lipopolysaccharide [LPS]).[1] In 2007, we named this "secretory hyperresponsiveness" to denote that the ferret airway produced dramatically increased mucus secretion in response to a known secretagogue. Unbeknownst to us at the time, Webber and colleagues[2] first used this term in 1997, to describe greatly increased mucus secretion with platelet-activating factor stimulation, remarkably also in the ferret trachea.

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Bronchial hyperresponsiveness (BHR) is a term generally used to describe increased airway smooth muscle contraction producing obstruction in people with asthma. In the pulmonary function laboratory, BHR is usually measured by bronchoprovocation tests using drugs like methacholine or osmotic agents, exercise, or cold air. The airway responds to these challenges not only with smooth muscle contraction but also with mucus secretion. Thus, although BHR involves each of these phenomena, because BHR is defined by the smooth muscle contraction, we use the term secretory hyperresponsiveness to refer to the increased mucus secretion. Unlike smooth muscle contraction, which is rapidly reversible using a bronchodilator, mucus hypersecretion produces airflow limitation that is more slowly reversible as secretions are cleared from the airway. While bronchospasm and its reversal with bronchodilators are straightforward measurements, secretory hyperresponsiveness is more difficult to quantify and is, thus, underrecognized.

Some people with asthma have a more predominant secretory response. This includes patients with middle lobe syndrome and airway obstruction because of mucus secretions, severe and fatal asthma, and possibly those with cough-dominant asthma (CDA). Secretory hyperresponsiveness also is a component of lung cancer associated with bronchorrhea. An extreme form of secretory hyperresponsiveness may lead to plastic bronchitis (PB), a condition characterized by rigid mucus bronchial casts that obstruct the airway.

Physiology of Mucus Hypersecretion

In health, mucus is secreted to coat the airway, prevent water loss, and trap inhaled material, which is removed by mucociliary clearance. Normal mucus is a mixture of mucin glycoproteins, electrolytes, water, and secreted lipids and peptides. Mucins are linearly linked core proteins encoded by mucin (MUC) genes. These core mucin proteins are heavily glycosylated. Of the identified human MUC genes, 11 are expressed in the airway at the messenger RNA or protein level. The principal airway gel-forming mucins are MUC5AC and MUC5B.[3]

Although acute mucus secretion is an effective airway defense, pathologic mucus hypersecretion and poor mucus clearance can lead to airway obstruction. Mucus secretion is increased in response to inhaled allergens, irritants including tobacco smoke, and infectious agents.[4] There can also be a chronic response with increased basal secretion rate and goblet cell hyperplasia.[5]

Mucins are stored in a highly compacted state in cytoplasmic granules of airway goblet cells and submucosal glands.[6] As the calcium in the granular contents dilutes, the compacted polyanionic mucin threads expand many hundredfold, filling the airway lumen. If the trigger remains or is repetitive, continued exocytosis is stimulated, resulting in hyperplasia, hypertrophy, and metaplasia of goblet cells or hyperplasia and metaplasia of submucosal glands.

Mucus accumulation in the airway can be the result of increased mucin production and secretion[7] or decreased mucociliary clearance.[8] Degradation can change mucin concentration after secretion. Airway mucins from patients with cystic fibrosis (CF) are rapidly degraded by bacterial serine proteases[9] causing a profound reduction in the mucin concentration.[10] During an exacerbation of asthma, there is inhibition of normal protease-driven mucus degradation leading to mucus accumulation; however, mucin degradation is restored during recovery.[11] In patients with COPD, we noted that protease-driven mucus degradation is inhibited at the beginning of an exacerbation and is restored during recovery (M. O. Henke, MD, unpublished data, 2009).

Mucin production and secretion can be initiated by signaling through the epidermal growth factor receptor (EGFR) activated by epidermal growth factor and also by transforming growth factor α, heparin-binding epidermal growth factor, amphiregulin, epiregulin, and β-cellulin. Each of these activators begins as proligands that are cleaved by proteases to release the active ligand to create the larger active complex with EGFR.[12] Many stimuli have been shown to increase the expression of these EGFR ligands but the mechanism of this expression has not been elucidated.[13] Mucin secretion can also be initiated by and signaled through the Toll-like receptors as part of the innate immune response. This has been established as important for host defense against gastrointestinal parasites[14] and in cancer.[15] This also appears to be a key mechanism for mucin production in airway bacterial infections.

Downstream of both EGFR and Toll-like receptor signaling, phosphorylation of the extracellular-regulated kinase (ERK) 1/2 with subsequent activation of transcription factors like nuclear factor κB is a common signaling pathway leading to mucin production and secretion. Mucoregulatory medications like the 14- and 15-member macrolide antibiotics that decrease excessive mucin production appear to do so by inhibition of ERK phosphorylation.[16]

Tobacco smoke exposure can induce mucin production and goblet cell hyperplasia in part due to generation of reactive oxygen species (ROS). Induction of mucin production by tobacco smoke is (1) the result of ROS activation of EGFR through ERK phosphorylation activating the Fra-2 transcription factor and (2) via c-Jun N-terminal kinases through JunD activation in an EGFR-independent signaling cascade that is also ROS initiated.[17] ROS generated by tobacco smoke or by xanthine/xanthine oxidase can also activate EGFR, resulting in goblet cell proliferation and increased MUC5AC gene and protein expression.[18]

IL-13 and Mucus Hypersecretion in Asthma

Patients with asthma who have chronic cough and sputum production have worse clinical control as measured by the Asthma Control Questionnaire (ACQ) and more frequent exacerbations[19]; additionally, there is dramatic mucus obstruction in the airways of patients with asthma who are dying.[20,21] Helper T-cell type 2 cytokines, including IL-13, are implicated in mucus production and goblet cell hyperplasia in asthma,[22] and IL-13 induces goblet cell hyperplasia with mucus hypersecretion in the mouse airways.[23] IL-13 also induces goblet cell hyperplasia in human airway epithelial cells in vitro.[24]

Airway goblet cell hyperplasia induced by IL-13 is steroid insensitive[25] but can be attenuated by 14- and 15-member macrolide antibiotics by inhibition of ERK phosphorylation.[26] These data are consistent with clinical reports that there is IL-13 overexpression in bronchial tissue and induced sputum from patients with severe asthma.[27] In patients with steroid-resistant asthma, increased IL-13 messenger RNA expression is not reduced by steroid inhalation.[28]

There is evidence that IL-13 can induce goblet cell hyperplasia via the IL-13 receptor α_1-Janus kinase-signal transducer and activator of transcription 6 (JAK-STAT6) pathway independent of EGFR signaling.[29] However, it has also been reported that EGFR signaling can enhance goblet cell hyperplasia by IL-13 because administration of the EGFR inhibitor, BIBX1522, can decrease goblet cell hyperplasia in mice given IL-13.[30] Because mucus hypersecretion in severe asthma appears to be largely regulated by IL-13 and is often steroid resistant, inhibition of IL-13 has been proposed as a potential target for novel therapy.[31]

Secretory Hyperresponsiveness in Clinical Practice

Allergic Bronchopulmonary Aspergillosis

Fungi in the genus *Aspergillus* are ubiquitous. They can be found wherever there is decomposing organic matter and on surfaces that get wet. Spores from some species in this genus, particularly *Aspergillus fumigatus*, can cause human disease. The spores are 2 to 3 μm in diameter, small enough to reach the alveoli in humans. Host defenses are normally able to clear *Aspergillus* spores without disease but hosts with propensity for airway mucus plugging, such as patients with asthma, are susceptible to mycotic colonization. One disease that can develop from this colonization is allergic bronchopulmonary aspergillosis. The mucus hypersecretion creates airway obstruction, expectoration of brown mucus plugs, and pulmonary infiltrates on chest radiograph. The impacted and expectorated plugs are made up of layered mucus, inflammatory cells (primarily eosinophils), and cellular debris. Charcot-Leyden crystals can be abundant but fragmented fungal hyphae may be the only fungal evidence. The airway tissue demonstrates asthma-like remodeling with inflammatory infiltrates, goblet cell hyperplasia, squamous metaplasia, and thickening of the basement membrane.[32]

MUC5AC expression has been closely associated with the epithelial cell immune response with a serine protease from *A fumigatus* being an essential trigger of mucin synthesis. This MUC5AC expression is dependent on *Aspergillus* triggering activation of cellular tumor necrosis factor (TNF)-α-converting enzyme, cleavage of membrane-bound TNF-α, and transactivation of the EGFR. EGFR-neutralizing antibody blocks MUC5AC expression and treatment with a serine protease inhibitor prevents TNF-α-converting enzyme activation.[33]

Asthma

Airway mucus hypersecretion has long been recognized as an important cause of death in asthma, and widespread airway mucus plugging has been consistently identified in asthma autopsy studies.[34] CDA, sometimes referred to as cough-variant asthma, appears to be associated with mucus hypersecretion. CDA is characterized by a prolonged nonproductive cough with variable response to bronchodilator therapy. Although the degree of airway narrowing is modest,[35] the airways in CDA show structural changes of goblet cell hyperplasia.[36] Sputum production is more prevalent in patients with CDA than in control subjects.[37] CDA appears to be a more common cause of chronic cough in children living in countries with higher levels of tobacco smoke exposure and air pollution, suggesting that this may be a harbinger of COPD. Secretory hyperresponsiveness in CDA would be consistent with this speculation.

There is goblet cell hyperplasia and submucosal gland hypertrophy in asthmatic airways that can be seen even in some patients with newly diagnosed asthma[38] and in most,[39] but not all,[40] patients with moderate asthma; mucin levels are higher in secretions from asthmatic as compared with normal airways.[41] The helper T-cell type 2 cytokines IL-9 and IL-13 have been associated with mucus hypersecretion and severe asthma.[42-44] Clinical data confirm the overexpression of IL-13 in severe asthma,[27] and experimental evidence suggests that corticosteroids not only do not inhibit the effects of IL-13 on goblet cell differentiation, but under some circumstances, they may also further increase IL-13 induced mucin production.[25,26]

Other mechanisms may contribute to increased mucus production in asthma. These involve inflammatory mediators, including secretory phospholipases A2,[1] LPS,[45] neutrophil elastase,[46] TNF-α, and IL-1β,[47] which regulate *MUC* expression and mucin secretion. Mucin gene expression, can be increased by inflammatory mediators released in chronic asthma.[48] Inflammatory mediators, abundant during allergy-related respiratory disease, may alter *MUC5AC* expression.[46,49-51] When patients have a positive airway provocation challenge test with methacholine or histamine but fail to reverse fully and rapidly with the use of an inhaled bronchodilator, this may be due, in part, to mucus hypersecretion causing persistent obstruction.

Chronic Cough and Protracted Bacterial Bronchitis

Inflammation in conducting airways with wet cough lasting >4 weeks is referred to as a protracted bacterial bronchitis (PBB).[52] Bacterial colonization of the airway is thought to be responsible for the persistent cough. Impaired mucociliary clearance, especially after viral infections, seems to be a significant risk factor for the establishment of bacterial infection.[53] Children with PBB have mucus and neutrophils but no frank purulence in bronchial lavage fluid.[54,55] PBB may respond to antibiotics.[56] The characteristic wet cough suggests that PBB is in part a manifestation of increased secretions. Histologic signs of chronic airway disease, including mucus obstruction, goblet cell hyperplasia, and chronic inflammatory cell infiltration, have been reported.[8,57]

COPD

Chronic productive cough has historically been felt to be a manifestation of secretory hyperresponsiveness in the subset of patients with COPD commonly called chronic bronchitis. The etiologic association of this phenotype with cigarette smoking and environmental exposures has confounded any conclusive assessment of an association between COPD and mucus hypersecretion. The "British hypothesis" advanced the theory that smoking caused mucus hypersecretion and impaired lung defense mechanisms and these two effects fed into a cycle of obstruction, infection, and parenchymal damage. Others believed that mucus hypersecretion in some with COPD was a primarily a nuisance and did not contribute to disease progression.

Epidemiologic studies beginning in the mid-1980s showed a correlation between COPD progression and chronic cough with sputum production.[58,59] Histologic studies have confirmed mucus obstruction in the distal airways of patients with COPD, even those without chronic productive cough.[60,61] The Copenhagen City Heart Study retrospective data analysis suggests that chronic mucus hypersecretion was significantly associated with both greater FEV_1 decline and an increased risk of hospitalization.[59,62] COPD exacerbations are associated with goblet cell hyperplasia,[63] mucus hypersecretion,[64] and "mucus plugging" in the airway lumen.[65] In COPD, chronic mucus hypersecretion has been shown to be an independent risk factor for death from obstructive lung disease.[66] In a study analyzing the severity of luminal occlusion in resected lung tissues from patients with COPD after lung volume reduction surgery, it was found that subjects with the greatest luminal occlusion died earlier than subjects who had the least occlusion.[67]

Cholinergic nerves are the dominant neural stimulant to mucin secretion in the airways.[68] Mucin secretion is mediated via muscarinic M3 receptors on the secretory cells, with water secretion mediated via M1 receptors.[69,70] Stimulation with cholinergic agonists can increase mucociliary clearance.[71-73] Anticholinergics block muscarinic receptors on airway secretory cells and smooth muscle and so, theoretically in COPD, may reduce vagal tone and mucus secretion and facilitate cough-induced mucus clearance.[74-76] Consistent with this suggestion is the observation that oxitropium bromide reduces the amount of mucus secretion in patients with COPD.[77] However, the onset of inhibition was slow and the mechanism by which it was mediated was unclear. Effects on mucociliary clearance with ipratropium bromide in patients with COPD have been difficult to demonstrate.[78] In fact in one study, tiotropium bromide reduced the effectiveness of cough for clearing mucus from the airways compared with placebo.[79] This may reflect changes in airflow dynamics

caused by bronchodilation, or altered depth of airway secretions following treatment.

Plastic Bronchitis

PB is a disease characterized by the formation of branching airway casts that are cohesive and quite different from the purulent sputum plugging described in CF.[80] Patients will sometimes expectorate large casts of their tracheobronchial tree. The casts can cause mild symptoms or can be life-threatening. The diagnosis may overlap with diseases such as asthma, and the airway plugging sometimes seen in allergic bronchopulmonary aspergillosis, although PB is characteristically refractory to asthma therapy.[80,81] Diseases such as congenital heart disease with single ventricle physiology, lymphatic anomalies, influenza infections, and sickle cell acute chest syndrome have all been associated with PB.[80-85]

PB is currently classified based on underlying disease. Casts from patients with structural congenital heart disease, especially with Fontan physiology, can be mucinous or chylous. Lymphatic disorders are generally associated with chylous casts and can accompany congenital heart disease. People with PB and atopy usually have eosinophilic casts with Charcot-Leyden crystals in a fibrinous background. These casts appear similar to those seen in severe asthma. Sickle cell acute chest syndrome is associated with fibrinous casts surrounded by a thin, yellow-colored fluid.[81]

The clinical management of PB comes primarily from observational reports. PB is not likely to be a single disease so therapy is not likely to be uniformly effective. When there are abnormalities of lymphatic flow to the heart, thoracic duct ligation has decreased cast formation; in patients with cardiac disease, Fontan physiology, and heart failure, cardiac transplantation leads to resolution of cast formation. All casts appear to contain inflammatory cells regardless of underlying disease. Those that have eosinophils are often associated with chronic eosinophilic bronchitis and only occasionally with true asthma. Fibrinolytic agents have been used to acutely reduce cast burden[86] and aerosol heparin has been used to decrease fibrin leak, presumably by inhibiting Tissue Factor.

Recurrent Atelectasis, Middle Lobe Syndrome

Atelectasis can result from obstruction of bronchial airflow due to intrinsic airway narrowing, mucus secretion, airway compression, or surfactant dysfunction. Obstructive atelectasis is the most common type and results from alveolar gas absorption when communication with the major airways is obstructed.[87] Mucus hypersecretion contributes to recurrent or persistent atelectasis primarily in patients with the middle lobe syndrome (MLS).

MLS is characterized by persistent or recurrent atelectasis of the middle lobe, lingula, or both.[88] Atelectasis of the middle lobe may persist for months, and repeated episodes of infection, inflammation, and obstruction may lead to bronchiectasis. MLS is often thought to be due to asthma.[89] In a case-control study, 53 children with persistent MLS were compared with subjects with current asthma without MLS and to nonasthmatic control subjects.[88] A positive response to methacholine bronchial challenge was more prevalent among children with MLS, even when compared with subjects with known asthma, despite the fact that the prevalence of sensitization to common inhaled allergens was similar among patients with MLS and those without asthma. These findings suggest that in children with MLS, factors other than allergic inflammation are responsible for BHR. It may be that in people with MLS, methacholine produces airflow obstruction because of mucus plugging rather than bronchospasm. These data may provide insight as to a cause of BHR in people who do not have asthma.[90]

Tumors

There are a number of lung tumors, primarily adenocarcinomas that can cause mucus hypersecretion. Severe bronchorrhea is reported in invasive mucinous adenocarcinoma, also called mucinous bronchoalveolar carcinoma.[91] The nomenclature for lung tumors has undergone recent changes to address advances in cytogenetics, molecular biology, immunohistochemistry, and therapy. In 2004, the World Health Organization (WHO) updated the classification system[92] for invasive malignant epithelial lung tumors. There are five variants of adenocarcinoma and a mixed type of the adenocarcinoma subtype "solid adenocarcinoma with mucin production": mucinous ("colloid") adenocarcinoma, mucinous cystadenocarcinoma, signet ring adenocarcinomas, fetal adenocarcinoma, and clear cell adenocarcinoma.[93] Additional mucus-secreting tumors include mucoepidermoid carcinoma (MEC) and mucinous bronchoalveolar carcinoma (BAC). More recently, the International Association for the Study of Lung Cancer, American Thoracic Society, and the European Respiratory Society sponsored an international multidisciplinary classification specifically for adenocarcinomas.[94] The terms BAC and mixed subtype adenocarcinoma are

no longer used. Mucinous BAC is now called invasive mucinous adenocarcinoma.

This 2011 classification proposal is, in part, based on literature supporting the finding that EGFR inactivation with monoclonal antibody inhibitors or tyrosine kinase inhibitors (TKIs) has demonstrated meaningful antitumor activity in some patients with adenocarcinomas.[95-97] Data from 223 patients enrolled in five separate clinical trials demonstrated that EGFR-TKI treatment in those with EGFR mutations was associated with a 67% response rate and a time to progression of 11.8 months. Importantly, EGFR genotype was more effective than clinical characteristics at selecting appropriate patients for consideration of first-line therapy with an EGFR-TKI.[98]

A study of the pathophysiology of each mucus-secreting tumor is beyond the scope of this review; MEC, however, can be demonstrative. MEC is a salivary gland tumor and not an adenocarcinoma. Although this type of mucus-secreting tumor is common in the salivary glands, it is extremely rare in the lung. It has a reported incidence of 0.1% to 0.2% of all lung tumors and has preponderance in the pediatric age group. Cytogenetic studies have drawn attention to translocations involving the pro-oncogene *cyclin-D1* and dysregulation of Notch signaling as explanations for the unchecked cellular reproduction.[99,100] This tumor usually presents as an intraluminal polypoid mass causing luminal occlusion, typically, of the large airways. The presenting symptom is of airway obstruction, and there is usually a history of recurrent pneumonia. Current therapy for bronchial MEC is surgical and largely curative but metastatic disease is described and clinical follow-up is necessary.[101] EGFR inactivation with specific TKIs has demonstrated meaningful antitumor activity in patients with MEC. In 2009, Han and colleagues[102] demonstrated an EGFR mutation in two of five cases studied and response to EGFR TKI in one case without an EGFR mutation or evidence of amplification.

The significance of mucins in oncology then is not limited to the obstructive symptoms caused by the mucus hypersecretion. The antitumor activity of EGFR inactivation is just one example of the role of mucin in neoplastic disease. Further immunohistochemical studies have demonstrated that expression of certain core mucin proteins can be correlated with the aggressiveness of tumors and can be used as a marker for the detection of precancerous and neoplastic conditions.[103]

Therapy

Management of secretory hyperresponsiveness involves identifying underlying causes and treating these when possible, reducing exposure to irritants like tobacco smoke, and potentially using mucoactive medications and airway clearance therapy; although for most of these conditions, data are few (Table 1).

Medications

Medications used to alter the properties and volume of mucus and sputum are referred to as mucoactive medications. This broad term includes mucolytic drugs that degrade mucin polymer bonds or the DNA-actin bonds in sputum. Mucolytics are meant to promote mucus clearance. With the exception of dornase alfa (which is specific for DNA polymers in sputum and pus and has only been shown to be effective in the treatment of CF), few drugs have been shown to be beneficial in treating mucus hypersecretion or retention.[104] N-acetylcysteine given orally is ineffective in promoting mucus clearance in patients with chronic bronchitis.[105] In people with COPD, there are no clinically important improvements in lung function or quality of life with mucolytic therapy.[106]

Expectorants are intended to increase the volume of secretions, making them easier to expectorate. Medications like guaifenesin (Robitussin, Mucinex) are meant to promote secretion clearance in patients with either acute or chronic airway disease but studies have failed to show that these are clinically effective.[107,108] However, hypertonic saline (7% saline for CF) and dry powder mannitol have been shown to be effective in promoting sputum clearance in people with CF or non-CF bronchiectasis, probably by inducing an effective cough and drawing water into the airway surface liquid, unbinding secretions that are stuck to the epithelium.[109,110]

Secretions appear to stick to the airway epithelium in part because of surfactant inactivation. The surface tension of secretions in chronic bronchitis and in CF sputum is much higher than normal mucus; aerosol surfactant has been shown to be effective in improving pulmonary function and promoting sputum clearance in people with chronic bronchitis.[111]

The mucoregulatory medications should be specific for secretory hyperresponsiveness as they reduce mucus hypersecretion. Anticholinergics are bronchodilators, and they also have a direct effect on secretions, reducing muscarinic-driven hypersecretion without changing the viscosity of secretions.[112] Aerosol oxitropium bromide has been shown to significantly decrease the volume of airway

TABLE 1] Mucus Hypersecretion Treatment Summary

Treatment	Advantages	Disadvantages
Medication classes		
Mucolytics	Only dornase alfa has been shown to be effective (in infected sputum in CF).	Few drugs demonstrate a benefit for treatment of mucus hypersecretion or retention.
		No clinically important changes seen with COPD.
Expectorants	Hypertonic saline and dry powder mannitol are shown to be effecting in promoting sputum clearance in CF and non-CF bronchiectasis.	Studies have failed to show clinical benefit from medicines like guaifenesin.
Aerosolized surfactant	Improves pulmonary function and promotes sputum clearance in chronic bronchitis.	Off-label use.
Anticholinergics	Reduce muscarinic-driven hypersecretion.	
	Does not increase the viscosity of secretions.	
Macrolide antibiotics	Decrease inflammation-driven hypersecretion.	Off-label use.
	Do not decrease the protective baseline level of mucus secretion.	
EGFR inhibitors	Show promise in inhibiting mucus hypersecretion associated with secretory adenocarcinomas.	Off-label use.
	Show potential for decreasing mucus hypersecretion from cigarette smoke and irritant-induced hypersecretion.	
Aerosolized tPA	Show promise for acute improvement of plastic bronchitis.	Off-label use.
		Expensive.
		Can be irritating to the airway.
Aerosolized heparin	Effective in patients with plastic bronchitis.	Off-label use.
	Shown to reduce mucin secretion.	No effect on preformed fibrin.
	Has antiinflammatory properties.	
	Little irritation to the airway.	
	Relative low cost.	
Devices		
High-frequency chest wall compression	No therapist needed.	Risk of mobilizing secretions in person with weakness or impaired cough.
	Less reliant on active participation.	Few long-term studies evaluating use.
	Can be used in toddlers.	
	Useful in people with an effective cough.	
	Promotes sputum expectoration.	
OPEP (eg, Flutter, Quake, Cornet and Acapella)	No therapist needed.	No long-term studies demonstrating clinical benefit.
	Promotes sputum expectoration.	Active participation required.
Sound-generating oscillatory airflow device (Lung Flute)	Can induce sputum in chronic bronchitis.	No published studies demonstrating benefit in airway disease.
		Active participation required.

(Continued)

TABLE 1] *(continued)*

Treatment	Advantages	Disadvantages
Mechanical insufflator/ exsufflator (Cough Assist)	Effective when cough is ineffective.	May cause airway collapse in infants, small children and those with known airway malacia.
		May decrease secretion clearance and promote atelectasis by reducing airway diameter.

CF = cystic fibrosis; EGFR = epidermal growth factor receptor; OPEP = oscillatory positive expiratory pressure; tPA = tissue plasminogen activator.

secretions in patients with chronic bronchitis.[77] Similarly, atropine and other anticholinergics can decrease mucus hypersecretion in animal models of airway inflammation.[113]

The 14- and 15-member macrolide antibiotics have also been shown to attenuate mucus secretion, in part by inhibition of ERK1/2.[16,114] These drugs are mucoregulatory as they do not decrease the protective baseline level of mucus secretion but will decrease inflammation-driven hypersecretion. Although corticosteroids are effective antiinflammatory medications, they are less effective mucoregulators in neutrophil-driven airway inflammation.[25] Corticosteroids have no effect on IL-13-induced goblet cell metaplasia and mucin hypersecretion.[25] On the other hand, the macrolide antibiotics have been shown to effectively reduce both IL-13 and LPS-stimulated mucus hypersecretion.[26]

EGFR inhibitors also have potential for decreasing mucus hypersecretion.[13,115] EGFR is a common pathway for hypersecretion that is induced by cigarette smoke and irritants[116]; EGFR inhibitors have shown promise in inhibiting the mucus hypersecretion associated with the secretory adenocarcinoma as discussed earlier.

There have been several case reports that the inhalation of tissue plasminogen activator (tPA) can acutely improve plastic bronchitis, most probably through fibrin depolymerization. tPA is expensive and can be very irritating to the airway with hemoptysis or dyspnea being reported after inhalation, so it cannot be recommended for chronic use.[86] Inhaled heparin has also been effective in patients with plastic bronchitis. Heparin has no effect on preformed fibrin but has been shown to reduce mucin secretion and prevent Tissue Factor activation of the fibrin pathway. Heparin also has antiinflammatory properties and is less irritating to the airway and less expensive than other drugs.[117]

Devices

Physical therapy, when properly applied, has been shown to slow the decline in lung function in people with CF[118] but has not been shown to be more effective than other forms of airway clearance.[119] Airway clearance can also be promoted using high-frequency chest wall compression but this is useful only in people who have an effective cough. There is some risk of mobilizing of central airway secretions patients with weakness and impaired cough.[120] Although there are many high-frequency chest wall compression devices on the market, there are few long-term data evaluating their use.

There are even fewer data on the oscillatory positive expiratory pressure (OPEP) devices (Flutter, Quake, Cornet, and Acapella).[121-123] When studied in the pulmonary function laboratory with acute single application of OPEP, these devices promote sputum expectoration. However, there are no long-term studies demonstrating clinical benefit of using these devices.[124] Whether this is due to the devices being ineffective or to poor adherence is not clear. The Lung Flute (Medical Acoustics, LLC) is another form of an oscillatory airflow device. Although it is claimed that this device helps mobilize secretions by sound, this has not been demonstrated. The Lung Flute can induce sputum expectoration in patients with chronic bronchitis and is as effective as hypertonic saline inhalation for sputum induction.[125] There are no published studies demonstrating the benefit of the Lung Flute in patients with airway disease.

In people who have a weak or ineffective cough, the Cough Assist device (Philips Respironics/Koninklijke Philips N.V.) may promote airway clearance and expectoration. Case reports suggest that people who are intubated, those with profound weakness, and those who are unable to use chest wall compression devices, may benefit from the use of the Cough Assist. This device expands the chest with positive pressure, followed by a rapid negative pressure "exhalation" of air and secretions. This device should be used with caution in infants and small children with collapsible airways (especially collapsible pharyngeal airway) and in patients with

known airway malacia. Negative pressure can reduce airway diameter, not only decreasing secretion clearance, but also potentially promoting the development of atelectasis.

Summary

Mucus hypersecretion is a distinct component of many airway diseases including inflammatory diseases and some forms of airway cancer. Although mucus secretion is an effective airway defense, secretory hyperresponsiveness can lead to airway obstruction and poor clearance. Therapy targeted at inflammation may be less effective in decreasing pathologic hypersecretion. There is a need for effective mucoregulatory medications to treat secretory hyperresponsiveness.

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