Chapter 9

Mucus-controlling Drug Therapy
Drug Control of Mucus: A Perspective

- Mucociliary escalator is a major defense system
- Failure may result in mechanical obstruction of the airway
- Properties of mucus
  - Protective
  - Lubricative
  - Waterproofing
  - Entraps microorganisms
Clinical Indication for Use

- To reduce accumulation of airway secretions, improve pulmonary function/gas exchange, reduce infection/damage
- Diseases:
  - Cystic fibrosis (CF)
  - Chronic bronchitis
  - Pneumonia
  - Diffuse panbronchiolitis (DPB)
  - Primary ciliary dyskinesia
  - Asthma
  - Bronchiectasis
Clinical Indication for Use (cont’d)

- Consider after:
  - Therapy to decrease infection/inflammation
  - Removal of irritants (including tobacco smoke)
Physiology of the Mucociliary System

- **Source of airway secretions**
  - Gel layer
  - Periciliary layer
  - Surface epithelial cells
    - Pseudostratified, columnar, ciliated epithelial cells
    - Surface goblet cells
    - Clara cells
  - Submucosal glands
    - With serous and mucous cells
Physiology of the Mucociliary System (cont’d)

Terminology

- Mucoactive medications
- “Mucolytic”
  - Most medications mobilize secretions via method other than direct thinning of mucus
Physiology of the Mucociliary System (cont’d)

- **Surface epithelial cells**
  - 6000 goblet cells/mm² of normal airway
  - No *direct* innervation of goblet cells

- **Submucosal glands**
  - Provide airway surface mucin
  - Under parasympathetic control
Physiology of the Mucociliary System (cont’d)

Ciliary system

- 200 cilia per cell
- Effective (power) stroke
- Recovery stroke
- Functional surfactant layer separates periciliary fluid from mucus gel
Factors affecting mucociliary transport

- Chronic obstructive pulmonary disease (COPD)
- Airway drying (such as with the use of dry gas for mechanical ventilation)
- Narcotics
- Endotracheal suctioning
Physiology of the Mucociliary System (cont’d)

- More factors affecting mucociliary transport
  - Airway trauma
  - Tracheostomy
  - Cigarette smoke
  - Atmospheric pollutants (SO$_2$, NO$_2$, ozone) may transiently increase transport, especially at low concentration. At higher, toxic concentrations or with prolonged exposure these decrease transport rates
  - Hyperoxia and hypoxia
Physiology of the Mucociliary System (cont’d)

- Food intake and mucus production
  - No reported association between milk and dairy product intake and upper or lower respiratory tract symptoms of congestion or nasal secretion weight.
Nature of Mucus Secretion

- Healthy person secretes 100 ml/day
  - Clear, viscoelastic, sticky
  - All but 10 ml reabsorbed in lung

- Structure and composition of mucus
  - Two major classes of mucins
    - Secreted mucins
    - Membrane-tethered mucins
Epithelial Ion Transport

- Under normal conditions:
  - Healthy airway epithelia can absorb salt and water driven by an active sodium transport.
  - Normal epithelia can also secrete liquid into the periciliary fluid driven by an active chloride transport through ion channels and passively through aquaporins or water channels.
Mucus in Disease States

- Chronic bronchitis
- Asthma
- Bronchorrhea
- Plastic bronchitis
- Cystic fibrosis
Physical Properties of Mucus

- Adhesive forces
  - Attractive forces between mucus and the airway surface
Physical Properties of Mucus (cont’d)

- Cohesive forces
  - Attractive forces between like molecules
  - Spinnability
  - Rheology
    - Study of the deformation and flow of matter
  - Viscosity
    - Resistance of a fluid to flow
  - Elasticity
    - Ability of a deformed material to return to its original shape
Physical Properties of Mucus (cont’d)

- Mucus as a viscoelastic material
  - As a solid, a gel has elastic deformation, storing energy with applied force
  - As a liquid, a gel flows under applied force, losing (dissipating) energy
Physical Properties of Mucus (cont’d)

- **Spinnability (cohesivity) of mucus**
  - Ability of mucus to be drawn out into threads was initially identified for cervical mucus and termed “spinability”
Physical Properties of Mucus (cont’d)

- Non-Newtonian nature of mucus
  - In an ideal Newtonian liquid, the applied force to rate of flow remains constant with changing force
  - A non-Newtonian substance, such as mucus, has changing viscosity (defined as the proportionality constant of force to flow) with varying applied force (shear rate)
Mucoactive Agents

- Mucolysis and mucociliary clearance
  - Mucolytic agents decrease the elasticity and viscosity of mucus because the gel structure is broken down
  - Therapeutic options for controlling hypersecretion
    - Remove causative factors
    - Optimize tracheobronchial clearance
    - Use mucoactive agents when indicated
Mucoactive Agents (cont’d)

- Mucolytics and expectorants
  - Classic mucolytics reduce mucins by severing disulfide bonds or charge shielding
**N-Acetyl-L-cysteine (NAC)**

- **Indications for use**
  - Treatment of conditions associated with viscous secretions
    - Despite in vitro mucolytic activity and a long history of use, no data demonstrate oral or aerosolized NAC is effective for any lung disease.
  - Acetaminophen overdose
N-Acetyl-L-cysteine (cont’d)

● Mode of action
  ➢ NAC disrupts the structure of the mucus polymer by substituting free thiol (sulfhydryl) groups for the disulfide bonds connecting mucin proteins
N-Acetyl-L-cysteine (cont’d)

- Hazards
  - Bronchospasm
    - Less common with 10% solution
  - Mechanical obstruction of airway
N-Acetyl-L-cysteine (cont’d)

- Incompatibility with antibiotics in mixture
  - Sodium ampicillin
  - Amphotericin B
  - Erythromycin lactobionate
  - Tetracyclines (tetracycline, oxytetracycline)
  - Aminoglycosides
Dornase Alfa (Pulmozyme)

• Indications and use in CF
  - Dornase alfa is indicated for the management of CF, to reduce the frequency of respiratory infections requiring parenteral antibiotics, and to improve or preserve pulmonary function in these subjects
Dornase Alfa (Pulmozyme) (cont’d)

- **Mode of action**
  - Reduces viscosity and adhesivity by breaking down DNA

- **Dose and administration**
  - Available as single-use ampoule
    - 2.5 mg of drug in 2.5 ml
  - Should be refrigerated and protected from light
Dornase Alfa (Pulmozyme) (cont’d)

- **Dose and administration**
  - Available as single-use ampoule
    - 2.5 mg of drug in 2.5 ml
  - Should be refrigerated and protected from light

- **Dose and administration (cont’d)**
  - Usual dose is 2.5 mg daily
  - Delivered by one of the following tested and approved nebulizers:
    - Hudson RCI UP-DRAFT II OPTI-NEB
    - Acorn II nebulizer
    - PARI LC PLUS nebulizer
Dornase Alfa (Pulmozyme) (cont’d)

- **Adverse effects**
  - Little difference between dornase alfa (3%) and placebo (2%)
  - **Common side effects:**
    - Voice alteration
    - Pharyngitis
    - Laryngitis
    - Rash
    - Chest pain
    - Conjunctivitis
Dornase Alfa (Pulmozyme) (cont’d)

- Clinical application and evaluation
  - Based not only on lung function
  - Also based on a reduction in the number and severity of infectious exacerbations
  - Thus the need for antibiotics and hospitalization
F-Actin-depolymerizing Drugs: Gelsolin and Thymosin $\beta_4$

- Gelsolin, an 85-kD actin-severing peptide, has been shown to reduce the viscosity of CF sputum in a dose-dependent manner.

- Thymosin $\beta_4$ decreases sputum cohesivity in a dose-dependent and time-dependent manner.

- *In vitro* studies have shown that F-actin-depolymerizing agents along with dornase alfa result in greater reduction in sputum cohesivity and viscoelasticity than either agent alone.
Expectorants

- Iodide-containing agents
  - Iodide-containing agents (e.g., SSKI or super-saturated potassium iodide) are generally considered to be **expectorants**
  - Thought to stimulate the secretion of airway fluid
Expectorants (cont’d)

- Sodium bicarbonate
  - By increasing the local bronchial pH, sodium bicarbonate weakens the bonds between the side chains of the mucus molecule, resulting in lowering of the mucus viscosity and elasticity
  - Has not been clinically demonstrated to improved airway mucus clearance
Expectorants (cont’d)

- Guaifenesin
  - Generally considered an *expectorant*
    - May stimulate the cholinergic pathway and induce increased mucus secretion from the airway submucosal glands
    - Has not been demonstrated to be clinically effective in randomized controlled trials
**Expectorants (cont’d)**

- **Dissociating solvents**
  - Urea is a dissociating agent that can break ionic and hydrogen bonds
    - Disrupts the hydrogen bonds between the oligosaccharide side chains of the neighboring mucus molecules
    - May also decrease the interaction between DNA molecules
    - Mucolytic action of urea occurs only at very high concentrations of urea (3-8 mol/L)
      - Not appropriate for human use
Expectorants (cont’d)

- Oligosaccharides
  - Oligosaccharide side chains make up about 80% of mucin structure
  - Bonds are weak and can be disrupted by agents such as
    - Dextran
    - Mannitol
    - Lactose
Expectorants (cont’d)

- P2Y$_2$ Agonists
  - Chloride conductance through the Ca$^{2+}$-dependent chloride channels is preserved in the CF airway
  - The tricyclic nucleotides UTP and ATP regulate ion transport through P2Y$_2$ purinergic receptors
  - UTP aerosol increases transepithelial potential difference
    - There is active development of novel P2Y$_2$ purinergic receptor agonists for clinical use
Mucokinetic Agents

- Increase cough clearance by increasing expiratory airflow or by reducing sputum adhesivity and tenacity

- Bronchodilators
  - Increase ciliary beat, but this has little effect
  - May increase mucus production
Surface-active Phospholipids

- Thin surfactant layer between the periciliary fluid and the mucous gel
  - Prevents airway dehydration
  - Permits mucus spreading on extrusion from glands
  - Allows efficient ciliary coupling with mucus
  - More importantly, allows ciliary release from mucus once kinetic energy is transmitted

- Surfactant therapy has been shown effective in treating chronic bronchitis and CF
Mucoregulatory Medications

- Decrease mucus hypersecretion
  - Steroids
  - Indomethacin (Japan)
  - Anticholinergics
    - Atropine
    - Ipratropium bromide
    - Tiotropium
  - Macrolide antibiotics
Other Mucoactive Agents

- Antiproteases
  - It has been shown that neutrophil proteases cause a secretory response from submucosal glands with an increase in mucus production
  - $\alpha_1$-Antitrypsin
  - Recombinant secretory leukocyte protease inhibitor (rsLPI)
Other Mucoactive Agents (cont’d)

- Hyperosmolar saline
  - *May* increase FEV₁ in patients
  - Alternate effect is *decreased* FEV₁
  - Unpleasant taste; coughing may make it unsuitable for long-term use
Gene Therapy

- Centered on complementary DNA transfer of the normal CFTR gene in CF patients
- For gene transfer to be effective, the vector and its package must be
  - Nonimmunogenic
  - Stable to shear forces during aerosolization
  - Safe for transfected cells
- Viral vectors that have been studied include
  - Adenoviruses
  - Adeno-associated virus
  - Lentivirus
Using Mucoactive Therapy With Physiotherapy and Airway Clearance Devices

- Gravity
  - Not a primary mechanism for normal mucociliary transport
  - Postural drainage may show benefit when incorporated into conventional chest physiotherapy (CPT)
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- **Insufflation-Exsufflation**
  - Inflates the lungs with positive pressure followed by a negative pressure to simulate a cough
  - Cycle begins with inspiratory pressure 25 to 35 cmH\(_2\)O for 1 to 2 seconds, followed by an expiratory pressure of 30 to 40 cmH\(_2\)O for 1 to 2 seconds
  - Can be used with an oronasal mask or attached to an artificial airway
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- Active cycle of breathing and forced expiratory technique (FET) maneuver
  - Combination of
    - Breathing control (relaxed diaphragmatic breathing)
    - Thoracic expansion control (deep breaths)
    - Forced expiration technique from progressively increasing lung volumes
  - No documented studies showing benefit
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

● Autogenic drainage
  - Aims to "optimize" airflow in the various generations of bronchi to move secretions
  - Has not been demonstrated to be as effective as CPT in mobilizing secretions
Incorporates staged breathing starting with small tidal breaths from expiratory reserve volume (ERV), repeated until secretions "collect" in the central airways

Patients are instructed to suppress cough, and a larger volume is taken for a series of 10-20 breaths, followed by a series of even larger (approaching vital capacity [VC]) breaths, and followed by several huff coughs
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- **Exercise**
  - Causes increased sputum production compared with rest
  - Appears to augment bronchial hygiene
  - Should not substitute for other bronchial hygiene regimens
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

● Positive airway pressure techniques

  ➢ Can be effective alternatives to chest physical therapy in expanding the lungs and mobilizing secretions
    • Cough
    • FET
    • Pursed-lipped breathing
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- High-frequency techniques
  - High-frequency oscillation (HFO) of the air column in the conducting airways has been shown to enhance clearance of secretions
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- Oscillation of the airway
  - The FLUTTER
  - The Percussionator
Using Mucoactive Therapy with Physiotherapy and Airway Clearance Devices (cont’d)

- Chest wall oscillation
  - The Vest
  - Has been reported to be effective for secretion clearance in patients with CF
  - Conjecture is that this device has a role in lung expansion for patients other than those with cystic fibrosis in the acute care setting
Future Mucus-controlling Agents

- Thicker and denser strands of mucus would be moved more efficiently by ciliary contact and elastic recovery than would thin, low-viscosity solutions.
- Endotracheal aspiration of secretions using suction would be easier with low-viscosity mucus.
- Treatment of bronchial hypersecretion would be better aimed at *normalizing* the rheological properties of mucus to optimize transport.
  - Musospissic agents
Respiratory Care Assessment of Mucoactive Drug Therapy

- Before treatment
  - Level of consciousness (LOC)
  - Adequacy of cough
  - Need for bronchial hygiene
Respiratory Care Assessment of Mucoactive Drug Therapy (cont’d)

- During treatment and short term
  - Correct use of equipment
  - Airflow changes
  - Mucus production
  - Respiratory rate and pattern
  - Subjective response
  - Adverse reactions
Respiratory Care Assessment of Mucoactive Drug Therapy (cont’d)

- **Long term**
  - Number and severity of:
    - Infections
    - ER visits
    - Hospitalizations
  - Need for antibiotics
  - Pulmonary function testing
Respiratory Care Assessment of Mucoactive Drug Therapy (cont’d)

- General contraindications
  - Profound airflow compromise
    - $\text{FEV}_1 < 25\%$ predicted
  - Severely compromised:
    - $\text{VC}$
    - Expiratory flow
  - Gastroesophageal reflux disease (GERD)
  - Inability to protect airway
  - Acute bronchitis or exacerbation of chronic disease may leave patient less responsive to treatment