**Mucoactive agents**

**Gardenhire**

**Chapter 9**

**Terminology**
- **Mucus**
  - secretion from mucous membranes, including surface goblet cells and submucosal glands
- **Sputum**
  - expectorated secretions that contain respiratory tract, oropharyngeal and nasopharyngeal secretions, as well as bacteria and products of inflammation
- **Gel layer**
  - the upper, more gelatinous layer of the mucociliary system; it has properties of viscosity and elasticity; depth is 0.5-20 µm
- **Sol (periciliary) layer**
  - the lower, more watery layer of the mucociliary system; it has the property of viscosity; depth is 7-10 µm

**Terminology**
- **Glycoprotein**
  - the primary component of mucus and a high-molecular-weight glycoprotein; it gives mucus its physical/chemical properties e.g., viscoelasticity
- **Oligosaccharide**
  - a sugar that is the individual carbohydrate unit of glycoprotein
- **Mucolytic**
  - breaks down the structure of mucus, usually reducing viscosity and elasticity
- **Expectorant**
  - an agent that improves expectoration of respiratory secretions, usually by stimulation of bronchial gland output

**Mucus in Disease States**
- **Chronic bronchitis**
  - defined clinically by the volume of sputum expectorated over time
  - histological examination shows hyperplasia of submucosal glands and goblet cells
  - the number of goblet cells increases and there is hypertrophy of the submucosal glands as measured by the Reid index of gland to airway wall thickness ratio (usually this ratio is 0.25-0.35, however, in bronchitis, this ratio may become 0.40-0.80) - these hypertrophied submucosal glands produce excessive amounts of mucus
  - tobacco smoke is considered the most important predisposing factor to airway irritation and mucus hypersecretion; other factors include infections, pollutants and genetics

- **Asthma**
  - mucus hypersecretion can be a chronic feature of asthma and airway inflammation, or can occur only during an acute asthmatic episode
  - in acute episodes, ≈ 8% of patients will have bronchorrhea, discharging 100 ml + of sputum/day
  - one study found that as many as 80% of patients with asthma report increased sputum expectoration

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Mucus in Disease States

• Bronchorrhea
  – the production of watery sputum of 100 ml or more per day
  – may respond to mucoregulatory agents e.g. corticosteroids, H₂ antihistamines and macrolide antibiotics, which are more effective when bronchorrhea is associated with airway inflammation

• Plastic bronchitis
  – rare disease seen in children and adults
  – aka fibrous bronchitis and Hoffman's bronchitis
  – involves the formation of mucin casts that may fit bronchial distribution of an entire lobe
  – urokinase may be a helpful treatment

Mucus in Disease States

• Cystic fibrosis
  – hereditary disease affecting exocrine glands, including glands in the airway
  – airway mucus hypersecretion leads to bronchial obstruction and frequent respiratory infections
  – basic defect is a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) – involves an increase in Na⁺ absorption and a decrease in Cl⁻ secretion which probably leads to decreased water secretion and increased reabsorption of the periciliary fluid; this causes increased mucus adhesion and impaired mucociliary clearance
  – secretion retention leads to chronic bacterial infections with organisms such as S. aureus and P. aeruginosa

Physical Properties of Mucus

• Adhesive forces
  – adhesion refers to the attraction of unlike molecules
  – in the airway, this refers to the attractive and frictional forces between the mucus and the airway surface
  – adhesion severely reduces the ability to clear secretions by coughing
  – mucokinetics are either abhesives that reduce the adhesivity of secretions or agents that increase the power of the cough
  – mucolytics may also work in part by severing the bonding of mucus to epithelium

Physical Properties of Mucus

• Cohesive forces
  – cohesion refers to forces between like molecules
  – terminology
    - rheology – study of the deformation and flow of matter; the rheologic behavior of mucus is the way it responds to forces by deforming and/or flowing.
    - viscosity – measure of the resistance of a fluid to flow.
    - elasticity – measure of the ability of a deformed material to return to its original shape.
    - spinnability – the ability of mucus to be drawn into long threads by a standardized device and measured in millimeters

Physical Properties of Mucus

• Viscoelasticity of mucus
  – Because of its viscoelasticity, mucus behaves partially as a fluid and partially as a solid
  – As a fluid, mucus flows under the applied force supplied by the cilia
  – As a solid, mucus has elastic deformation under applied force
  – As the tips of the cilia contact the gel during the forward power stroke the mucus is stretched and its elastic recovery causes it to snap forward; at the same time, mucus flows forward as a fluid due to the forward beat of the cilia
Physical Properties of Mucus

- Mucolysis and mucociliary clearance
  - Mucolytic agents decrease the elasticity and viscosity of mucus by breaking down the gel structure.
  - Since elasticity is essential for mucociliary transport, mucolytics can have a negative effect—liquefying secretions too great an extent could lead to aspiration while suctioning.
  - The goal should be to optimize the viscoelasticity of the mucus and not just liquefaction.

Physical Properties of Mucus

- Options for controlling mucus hypersecretion
  - Remove causative factors where possible
    - Treat infections
    - Stop smoking
    - Avoid pollution and allergens
  - Optimize tracheobronchial clearance
    - Use bronchodilators if they increase airflow
    - Bronchial hygiene
      - Coughing, deep breathing exercises
      - PEP therapy
      - Postural drainage/Flutter valve
  - Improve airflow by exercise and good nutrition

N-acetyl L-cysteine (NAC)

- Indications for use
  - As a mucolytic, acetylcysteine has been used to treat conditions associated with viscous secretions (aerosol, direct instillation).
  - A 2nd use is as an antioxidant to reduce hepatic injury with acetaminophen overdose (oral).
  - Although excellent in vitro results of mucolysis have been demonstrated, and clinically many patients do increase sputum expectoration, there is still no concrete proof that acetylcysteine is effective therapy for any pulmonary disease; nevertheless, it remains a popular drug for treating viscous secretions.

N-acetyl L-cysteine (NAC)

- Dosage and administration
  - Acetylcysteine is used in solution for aerosol or for direct instillation into the tracheobronchial tree
    - Aerosol: 3-5 ml of the 20% solution tid or qid
    - Aerosol: 6-10 ml of the 10% solution tid or qid
    - Direct instillation: 1-2 ml of either the 10% or 20% solution

Note: Manufacturer’s guidelines should be followed when using disposable SVN; 6-10 ml may be an excessive amount for some devices.

N-acetyl L-cysteine (NAC)

- Mode of action
  - Acetylcysteine disrupts the structure of mucus by substituting free thiol (sulfhydryl) groups for the disulfide bonds in the mucus (Fig. 9-9, p. 179).
N-acetyl L-cysteine (NAC)

- **Mode of action**
  - The substituted groups do not provide a bond or cross-link between the strands and both the elasticity and viscosity of the mucus is reduced.
  - Viscosity reduction begins immediately upon physical contact and mucolytic activity increases with higher pH and is optimal at a local pH of 7.0-9.0.
  - Acetylcysteine contains ethylenediaminetetraacetic acid as a chelating agent.
  - Opened vials should be refrigerated and discarded after 96 hrs.
  - A light purple color indicates metal ion removal, but does not affect the safety or efficacy of the drug.

- **Hazards**
  - Most serious potential problem is bronchospasm:
    - More likely with hyperreactive airways.
    - More common with the 20% solution.
  - Occurrence can be lessened with concomitant use of a bronchodilator, which can be mixed with the acetylcysteine, or given before administration of the acetylcysteine – should use a bronchodilator with rapid onset and peak effect.
  - Other possible complications include:
    - Stomatitis.
    - Rhinorrhea.
    - Airway obstruction due to liquefied secretions.
    - Nausea and vomiting from odor/taste.

- **Antioxidant properties of acetylcysteine**
  - The antioxidant properties of thiols such as acetylcysteine may prevent pulmonary injury in patients with COPD, ARDS or lung cancer.
  - One study of 61 patients with mild to moderate lung injury showed that the IV administration of 40 mg/kg/day for 3 days improved systemic oxygenation and reduced the need and length of ventilatory support.

N-acetyl L-cysteine (NAC)

- **Incompatibility with antibiotics in mixture**
  - Acetylcysteine is incompatible in mixture with the following antibiotics and should not be combined in physical solution:
    - Sodium ampicillin.
    - Amphotericin B.
    - Erythromycin.
    - Tetracyclines.
    - Aminoglycocides.
  - The topical use of acetylcysteine in the lung does not preclude the administration of these antibiotics by any other route.

Dornase Alpha (Pulmozyme)

- **Indication for use**
  - Dornase alpha is indicated in the management of cystic fibrosis to reduce the frequency of respiratory infections requiring parenteral antibiotics and to improve or preserve pulmonary function in these patients.
  - The bulk and properties of respiratory secretions in cystic fibrosis are due in part to the presence of DNA material from necrosing neutrophilia present during chronic respiratory infections and to surfactant phospholipid hydrolysis by-products of inflammation.
  - In the presence of infection, neutrophils are attracted to the airways, degenerate and release DNA, which further increases the viscosity of secretions.
Dornase Alpha (Pulmozyme)

- **Indication for use**
  - DNA is an extremely viscous polyanion that is present in infected, but not in non-infected
  - DNA in secretions may also contribute to reduced effectiveness of aminoglycoside antibiotics such as gentamicin given by the inhaled route

Dornase Alpha (Pulmozyme)

- **Mode of action**
  - Dornase alpha reduces the viscosity and adhesivity of infected respiratory secretions when given by aerosol
  - this action is associated with a decrease in the size of the DNA in the sputum
  - the change in sputum viscosity is dose dependent – greater reduction occurs at higher concentrations of the drug

Dornase Alpha (Pulmozyme)

- **Dosage and administration**
  - Dornase alpha is available as a unit dose ampoule containing 2.5 mg in 2.5 ml of solution; the solution should be refrigerated and protected from light
  - the usual dose of dornase alpha is 2.5 mg daily by aerosol, delivered through one of the approved nebulizers
  - clinical trial results and laboratory information are only available to support use of the following nebulizer/compressor systems
    - other nebulizers may work, but delivery of aerosol dornase alpha requires a system capable of appropriate aerosol particle size and quantity

Dornase Alpha (Pulmozyme)

- **Recommended Nebulizer/Compressor Systems**
  - Hudson T Up-draft II with Pulmo-Aide
  - Marquest Acorn II with Pulmo-Aide
  - PARI LC Jet+ with PARI PRONEB
  - PARI BABY with PARI PRONEB
  - Durable Sidestream with Mobilaire
  - Durable Sidestream with Porta-Neb

Dornase Alpha (Pulmozyme)

- **Adverse effects**
  - common side effects
    - voice alteration
    - pharyngitis
    - laryngitis
    - rash
    - chest pain
    - conjunctivitis
  - less common side effects
    - respiratory
      - cough
      - dyspnea
      - pneumothorax
      - hemoptysis
      - rhinitis sinusitis
      - flu-like symptoms
      - malaise
      - GI obstruction
      - hypoxia
      - weight loss

Dornase Alpha (Pulmozyme)

- **Adverse effects**
  - during clinical trials, side effects with dornase alpha were little different from placebo and the discontinuance rate was similar – 3% with dornase alpha and 2% with placebo
  - contraindications include hypersensitivity to the drug
Expectorants – Iodide-containing agents

- Indications for use
  - indicated for their mucolytic/expectorant properties
- Modes of action
  - stimulation of bronchial glands – circulating I enters bronchial glands rapidly and stimulates these glands to secrete the characteristic low viscosity watery mucus; these secretions show iodide content very soon after oral administration - also stimulates nasal and salivary glands
  - stimulation of vagal reflex – iodides act like many other oral mucokinetics to stimulate the gastropulmonary mucokinetic vagal reflex; large doses can cause nausea and vomiting

Expectorants – Iodide-containing agents

- Modes of action
  - direct mucolytic effect – the addition of I to sputum in vitro results in a rapid decrease in viscosity - this particular action is not known - may be "lyotropic", where I alters the molecular configuration of mucoprotein strands - direct mucolytic effect may be equal to that of acetylcysteine
  - potentiation of proteases – normal respiratory tract fluid contains proteases liberated from polymorphs & other cells present in the fluid; these enzymes are capable of digesting mucoprotein, but normally not enough to notice; iodide potentiates the enzymatic activity of these proteases, facilitating the breakdown of mucus into a less viscous fluid

Expectorants – Iodide-containing agents

- Dosage and administration
  - most common prep is SSKI (saturated solution of potassium iodide) – standard SSKI strength is 1 gm/ml
  - other preps of KI range from app. 300-800 mg/ml
  - standard recommended dose of SSKI is 25-35 mg/kg/day in divided doses - most physicians order by drops - basic single dose order for adults is about 10 gtts (app. 1 ml or 1 gm or 1000 mg) this dose contains app. 6 mEq of K+ – should be given qid
  - some patients may not show results until 2-3 X this dose is administered
  - in alveolar proteinosis, favorable effect may be observed with 2-3 gm qid for a few weeks

Expectorants – Iodide-containing agents

- Adverse effects
  - metallic taste – may be reduced by taking medication with milk or juices
  - gastric irritation – may be reduced by taking the medication after meals
  - rhinitis – usually only a minor problem
  - increased salivation and swelling of the salivary glands
  - adolescents may develop acne-like skin eruptions – other rashes may develop
  - rarely, mucokinetic doses of iodides can result in hypothyroidism; very rarely, hyperthyroidism is caused

Expectorants – Iodide-containing agents

- Adverse effects
  - other side effects include: mental depression, nervousness, insomnia, Parkinsonism, headache and impotence
  - adverse effects can be expected in 10-15% of all pts. and in up to 40% of those pts on large dose therapy
  - all side effects subside when drug is DC’d
  - severe, adverse effects are rare, but O.D. can cause some extremely unpleasant and dangerous symptoms such as cardiac dysrhythmias
Expectorants – Salt Solutions

- Availability
  - Two most common salts used: ammonium chloride (NH₄Cl) and sodium citrate (Na⁺ citrate)
  - Both are found in many popular over-the-counter cough preparations, including:
    - Benylin cough syrup – 5 ml contains 125 mg NH₄Cl
    - Coricidin Cough Formula – 5 ml contains 100 mg NH₄Cl
    - Triaminicol cough syrup – 5 ml contains 90 mg NH₄Cl
    - Benylin cough syrup – 5 ml contains 50 mg Na⁺ citrate
    - Chlortrimeton cough syrup – 5 ml contains 50 mg Na⁺ citrate

Assessment of Mucoactive Drug Use

- Before treatment
  - Assess patient’s adequacy of cough and LOC to determine the need for suctioning equipment or the need for adjunct mucokinetic modalities (CPT, PEP therapy) and to determine if treatment is contraindicated
- During treatment and short-term
  - Instruct and verify correct use of nebulizer equipment
  - Assess therapy based on indications for the drug
  - Monitor patient for adverse effects such as a fall in FEV₁ and/or GERD
  - Assess breathing pattern and rate
  - Assess patient’s subjective reaction to therapy

- During treatment and short-term
  - Discontinue therapy if patient experiences adverse effects
- Long-term
  - Monitor number and severity of respiratory tract infections, need for antibiotic therapy, ED visits and/or hospitalizations
  - Monitor PFT for improvement or for slowing in the rate of deterioration
- General contraindications
  - FEV₁ <25% of predicted – could result in airway obstruction
  - Use with caution in patients with severely compromised VC and expiratory flows
  - Patients with acute bronchitis or exacerbation of a chronic disease may be less responsive to mucoactive therapy