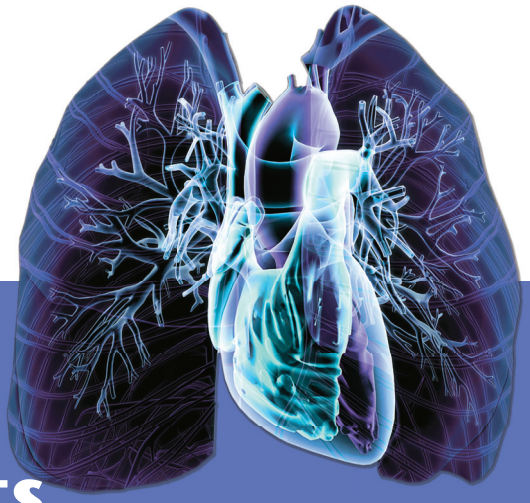
Chapter 6

Mucokinetics and Surfactants



OBJECTIVES

Upon completion of this chapter you will be able to

- Define key terms related to mucokinetic and surfactant agents.
- Describe the production, function, and clearance of mucus in the healthy lung.
- State the indications for bland aerosols and mucolytic agents.
- Compare and contrast the mechanisms of action of bland aerosols and mucolytic agents.
- Describe how surface tension relates to oxygenation and the work of breathing.
- Describe the role of surfactants in the lungs and surfactant replacement agents.
- Describe the mechanisms of action of expectorants and antitussive agents.

KEY TERMS

aliquot
bronchial gland
bronchorrhea
endogenous surfactant
exogenous surfactant
expectorant
goblet cell
hydrophilic
hypertonic
hypotonic
isotonic
maintenance therapy
rhinorrhea
stomatitis
surface tension
surfactant
viscoelastic

ABBREVIATIONS

ACCP American College of Chest Physicians
ARDS acute respiratory distress syndrome
DNase deoxyribonuclease
FVC forced vital capacity
NaCl sodium chloride, or salt
PDA patent ductus arteriosis
PEP positive expiratory pressure
RDS respiratory distress syndrome of newborns
SP surface proteins

This chapter encompasses a rather diverse group of drugs with widely varying effects. We will need to review the physiology of mucus production, mucus function, and the effects that various disease states have on them. We will look at the role of *bland* (unmedicated) aerosols and mucolytics and the importance of bronchial hygiene techniques in the management of retained secretions. The consequences of retained secretions can be very serious and include infections, airway obstruction, and collapse (atelectasis). It is therefore important to understand the pharmacologic aids available to you to assist in good bronchial hygiene.

Finally we will take a closer look at the lower respiratory tract, where surfactants play a critical role in maintaining the integrity of the alveolar surface. This integrity is vital to the role of adequate gas exchange and therefore must be maintained. This chapter will provide the reader with a basis for understanding current and future roles for surfactant replacement therapy.

6.1 THE MUCOCILIARY SYSTEM

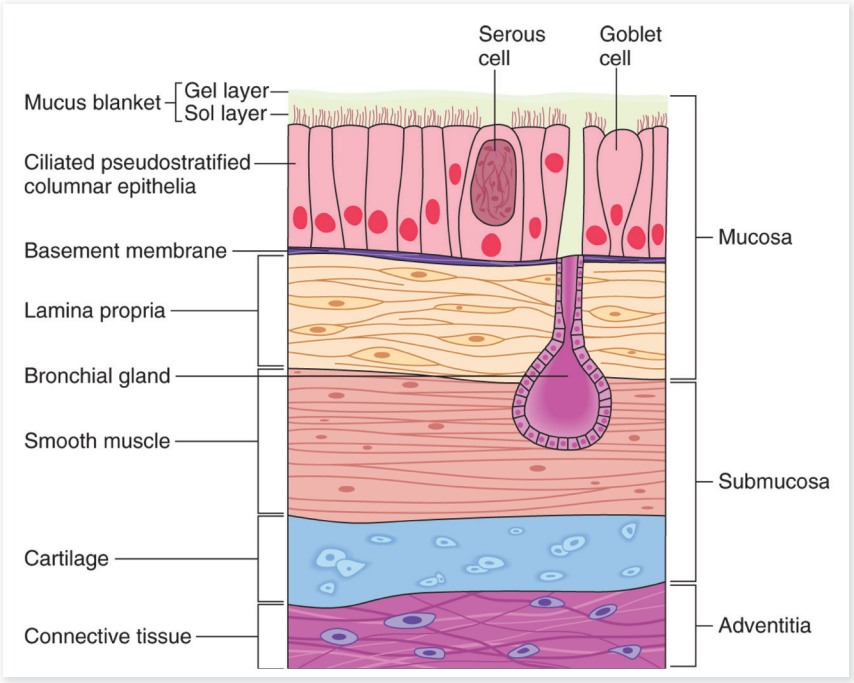
6.1a Anatomy and Physiology

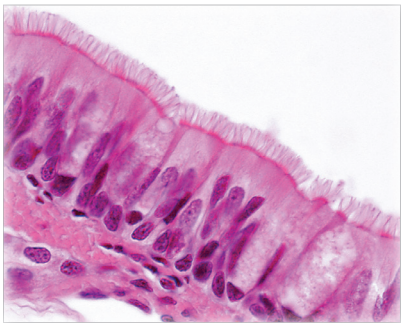
Learning Hint

The terms *mucous, mucus,* and *mucosa* are often confused. Mucus is a secretion of the mucous membranes or mucosa. For example the respiratory mucosa or mucous membranes secrete the substance mucus, which protects the airways.

The three layers of the airway are the mucosa, submucosa, and adventitia (see Figure 6-1). The mucosa (inner layer of the airway) is made up of different types of specialized epithelial cells, which rest on a basement membrane. Most numerous are the pseudostratified ciliated columnar epithelia, but there are also secretory cells such as goblet cells, serous cells, and clara cells. The goblet cells produce a relatively small amount of mucus, which is secreted into the airway. The serous cells produce less-viscous mucus, which makes up the sol layer of the mucus—we'll get to that in a minute. The role of the clara cells is not completely clear, but they are known to have a high degree of metabolic activity and to contain a lot of enzymes. The bronchial glands are found in the submucosal layer. They produce most of the mucus found in the airways. Together, the **goblet cells** and **bronchial glands** produce about 100 ml of mucus each day. Most of the mucus is reabsorbed, but about 10 ml reaches the pharynx each day, where it is usually swallowed.

FIGURE 6-1 Illustration of the Three Layers of the Airway and a Micrograph of the Respiratory Epithelium





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The mucociliary system, or mucociliary escalator as it is sometimes called, consists of the mucosal blanket that lines the airways from the naso- and oropharynx to the terminal bronchi. It also includes the cilia, which propel the mucus up the airway. Cilia are tiny hairlike projections that arise from the surface of the mucosal cells. There are about 200 cilia per cell, and they are about 6 microns in length. The cilia beat about 1,000 times per minute in a coordinated fashion to propel the mucus toward the upper airway. In healthy lungs, the mucus moves forward at a speed of about 2 cm/min.

The mucociliary system is an important part of the pulmonary defense system. It protects the lungs from inhaled debris, and it contains enzymes that give it antimicrobial properties that help prevent infection. Mucus helps to warm and humidify inspired gases, and it prevents excessive loss of heat and moisture from the airways. It is important to note that no cilia or mucus are found in the lower airways from the respiratory bronchioles to the alveoli.

Learning Hint

Exposure to irritants such as cigarette smoke increases the size and number of the bronchial glands, which accounts for the excessive mucus production and cough that many smokers have.

6.1b Structure and Composition of Mucus

The layer of mucus (or *mucosal blanket*) that covers the surface of the airways is about 5 to 10 microns thick and is made up of two distinct layers, the gel layer and the sol layer. The gel layer floats on top of the sol layer and is about 1 to 2 microns thick; as its name implies, it is rather gelatinous. It is sticky and works a lot like flypaper to trap inhaled particles and bacteria. The sol layer is deeper (about 4 to 8 microns thick) and has a more watery consistency, which enables the cilia to beat freely. The beating of the cilia within the sol layer helps propel the gel layer toward the larynx.

The mucus molecule itself is very large and complex. It is about 95% water, so it is imperative that there is a sufficient amount of water available in the body to produce normal mucus. Once mucus has formed, it does not absorb

Learning Hint

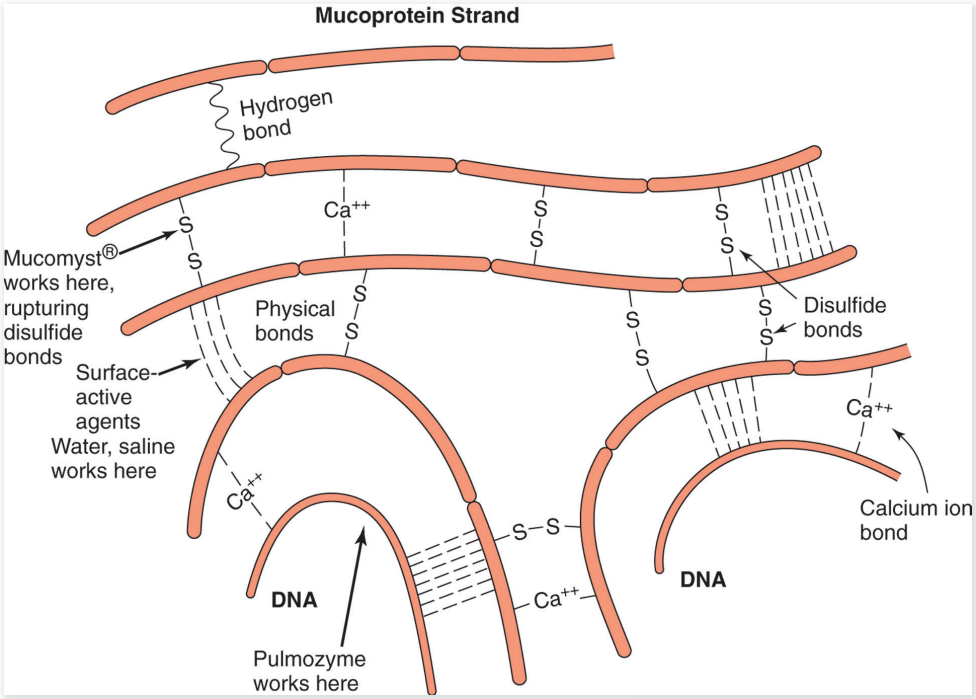
The consistency of the mucus plays an important part in mucus clearance. If mucus is too thick, it becomes very difficult for the cilia to move the mucus (think of trying to row a boat through pudding). Mucus that is too thin is not easily managed either. If your garage is flooded, would you use a rake to move the water to the floor drain?

Learning Hint

The structure of the mucus molecule has been compared to a round bottle brush, and the molecules tend to form long, flexible strands that are **hydrophilic**, meaning they attract water like a sponge. A general concept of the molecular structure will be helpful in understanding how some of the mucolytic agents work.

water readily. The remaining 5% of mucus composition comprises long, flexible strands of protein and lipid molecules that form polypeptide chains, with many carbohydrate side chains attached. The side chains are cross-connected with disulfide, physical, ionic, and hydrogen bonds (see Figure 6-2).

FIGURE 6-2 The Mucus Structure



See Table 6-1 for a summary of the functions of mucus in the healthy lung.

TABLE 6-1 Mucus Function in the Healthy Lung

Preventing water from moving into and out of the epithelia
Shielding epithelia from direct contact with toxic materials, irritants, and microorganisms
Preventing infection by the action of antimicrobial enzymes
Lubrication of the airway

Proper function of the mucociliary system is critical to the maintenance of a healthy pulmonary system. The volume, consistency, and structure of mucus produced can be altered in various disease states, including primary pulmonary disease and systemic dehydration. Mucus production increases when the respiratory tract is irritated and during increased parasympathetic stimulation. In certain disease states (such as cystic fibrosis, pneumonia, and chronic bronchitis), mucus production increases significantly. The airways can produce more than twice the normal amount of mucus. Simultaneously, mucus clearance can also be impaired, resulting in an overwhelming accumulation of mucus in the lungs. See Table 6-2 for a more complete listing of disease states that increase the volume and/or thickness of mucus.

TABLE 6-2 Diseases That Increase the Volume or Thickness of Mucus

Chronic bronchitis
Asthma
Cystic fibrosis
Acute bronchitis
Pneumonia

The frequency with which the cilia beat is also adversely affected by disease state, environmental conditions, and chemicals. Many factors can slow or stop the beating action of the cilia, which decreases the rate of mucus clearance from the lung. Thick mucus, dry gas, smoke (including cigarette smoke), noxious gases, infection, positive-pressure ventilation, foreign bodies (including endotracheal tubes), high concentrations of oxygen, and certain drugs such as atropine are all known to slow the beating of the cilia. Table 6-3 identifies factors that impair the function of the cilia.

TABLE 6-3 Factors That Impair Ciliary Activity

Endotracheal tubes
Extremes of temperature
High concentrations of oxygen
Dust, fumes, and smoke
Dehydration
Thick mucus
Infections

Either increased mucus production or impaired mucus clearance can result in a pulmonary system that is completely overwhelmed with thick, retained secretions that obstruct the airways. Although the mechanisms controlling mucus composition and production are not completely understood, the pharmacologic approach to secretion management generally falls into one of the following broad categories:

- Those that increase the depth of the sol layer (water or saline solution and expectorants)
- Those that alter the consistency of the gel layer (mucolytics)
- Those that improve ciliary activity (sympathomimetic bronchodilators and corticosteroids)

A variety of pharmacologic agents and bland aerosols alter the structure of mucus. Mechanical techniques such as deep breathing, assisted coughing, and suctioning can be applied to aid in the removal of secretions. Respiratory care practitioners are frequently called on to assist with mobilization of retained secretions by applying various combinations of humidity, bland and medicated aerosols, and mechanical techniques.

Of course the purpose of this chapter is to focus on the pharmacologic approaches for the control of mucus. This includes bland aerosols, which increase mucus clearance, mucus production, and productive coughing. Mucus-controlling drugs (mucolytics) achieve their effect by changing the molecular structure of the

mucus gel so that the cilia can work more efficiently. The pharmacologic basis for the mucus-controlling agents that are currently available will be reviewed in this chapter. Because mucus is composed largely of water, the importance of maintaining adequate systemic hydration has been emphasized as a very important aspect of maintaining proper consistency and clearance of mucus. See Table 6-4 for factors that lead to dehydration and thereby thicken mucus.

TABLE 6-4 Factors That Lead to Dehydration and Thick Mucus

Increased respiratory rate
Increased depth of breathing
Systemic fluid loss
Infections

CONTROVERSY

The Importance of Proper Hydration

While proper hydration is stressed in mucus clearance, good empirical evidence doesn't fully exist that supports this belief. While an older study, one small study in 1987 found no difference in sputum volume, elasticity, respiratory symptoms, or ease of expectoration among stable COPD patients who were fully hydrated, were dehydrated, or had a normal fluid intake (Shim et al., 1987).

PATIENT & FAMILY EDUCATION

It is important to emphasize to both patients and their families that COPD is an irreversible, chronic lung disease that generally worsens with time. The most important strategy to decrease mucus production in smokers is to stop smoking. Currently there are no medications, including the ones discussed in this chapter, that are capable of reversing the damage done to the lungs.

6.2 BLAND AEROSOLS

6.2a Definitions

Bland aerosols do not affect the mucus molecule directly; instead they dilute the mucus by altering its water content. They are also referred to as wetting agents. Bland aerosols include the following agents:

- Water
- Normal saline
- Hypotonic saline
- Hypertonic saline

Historically, treatment of thick, retained secretions has been aimed at thinning thick mucus by adding water or saline to the respiratory tract by inhalation. Once it has formed, the gel layer of the mucus is somewhat resistant to the addition and removal of water. However it is critical to have an adequate amount of water available as mucus is being formed so that the mucus will have normal **viscoelastic** properties (the ability to change from thick to thin and back).

Bland aerosols may not be as effective as once thought at thinning thick mucus by topical hydration or mixing; instead, their benefit may be due to a different mechanism. All bland aerosols are somewhat irritating to the airway (although they are not all equally irritating) and may have varying benefits; in some cases they may produce harm, depending on the patient's underlying disease. Irritation tends to increase the production of thinner mucus, possibly by stimulating the goblet cells' and bronchial glands' production of mucus. Mucus clearance is increased by restoring the sol layer and stimulating cough, and this effect can be clinically useful.

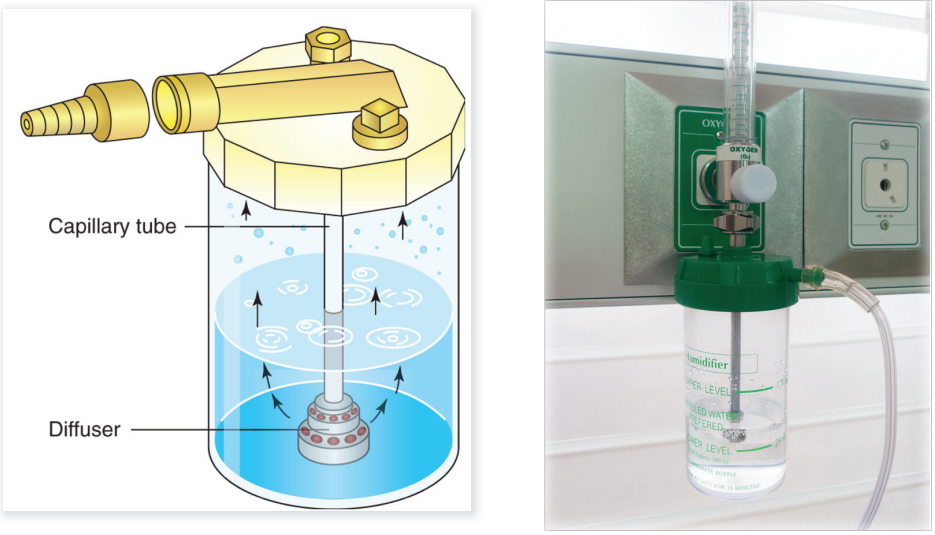
6.2b Delivery Methods

Several methods are available for delivering water and saline to the lung. One method is the use of humidification devices, which work by bringing dry gas into contact with water, where the gas passes over or bubbles through the water. The water molecules evaporate and therefore increase the humidity of the gas. Another method of delivering water to the airway is the use of nebulizers. Nebulizers produce aerosols, which are small droplets of solution suspended in a gas. When the aerosol is inhaled, water particles are deposited in the airway. The final method is to instill the liquid directly into the respiratory tract. We will discuss each of these techniques briefly.

Humidifiers

Simple humidifiers are used mainly for oxygen delivery (see Figure 6-3). The amount of humidity that they add to the gas is highly variable and depends on how long the gas is in contact with the water, the surface area available between the gas and the water, and the temperature of the gas. The type of humidifier commonly used in conjunction with oxygen therapy is intended to minimize the drying effects of oxygen, not to serve as therapy for thick secretions. Heating inspired gas greatly increases the amount of water vapor that the gas can carry. Systems that deliver heated, humidified gas are most often used with mechanical ventilators. In-depth knowledge of how to deliver and monitor gas that is heated to body temperature and 100% relative humidity is an important aspect of ventilator management.

FIGURE 6-3 A Simple Humidifier



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Aerosols

The most common method of administering water and saline solutions to the respiratory tract is by aerosol. Small-volume (handheld) nebulizers, large-volume nebulizers, and ultrasonic nebulizers have all been used. Small-volume nebulizers typically contain 3 to 5 ml of aerosol, of which only about 1 ml is actually deposited in the lung. For this reason small-volume nebulizers are used for medication delivery, as discussed in Chapter 4, and sputum induction, when stimulating the cough is the goal of the therapy.

Large-volume and ultrasonic nebulizers are capable of delivering significant volumes of aerosol to the lungs (see Figure 6-4). Although they are clinically very useful, ultrasonic nebulizers have been shown to cause runny, watery secretions in infants. Secretions of this consistency also impair the function of the mucociliary system. This condition has been, again, compared to trying to rake water.

Direct Instillation

Direct instillation of fluid (usually normal saline) into the respiratory tract is sometimes performed on patients with artificial airways, during bronchoscopy, and on rare occasions through a transtracheal catheter. Fluid injected into the upper airway is very irritating and causes a strong cough.

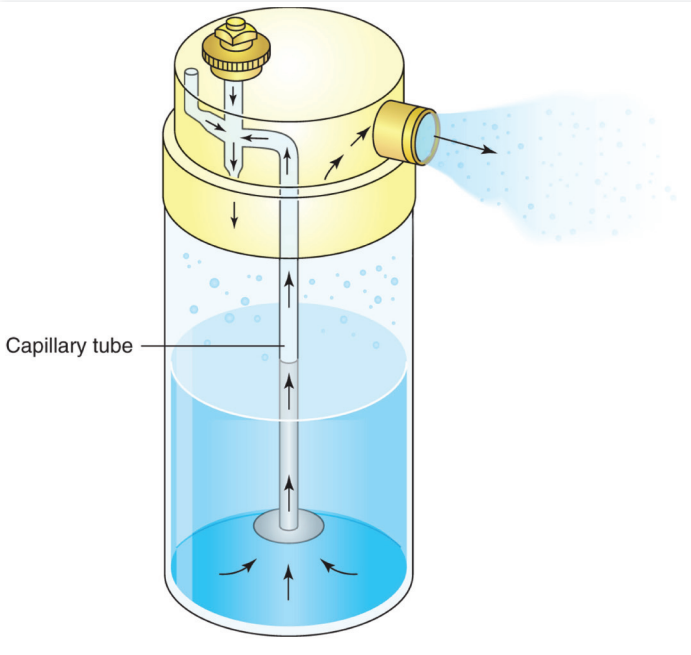
The once-common practice of *routinely* instilling saline into the airway during suctioning is now discouraged. It was once thought to improve mucus clearance by thinning thick secretions, but it is now understood that the saline does very little to thin thick secretions, and only about 20% of the instilled fluid is recovered during suctioning. Current evidence suggests that instilling saline down the endotracheal tube dislodges large numbers of bacteria from the inside of the patient's endotracheal tube into the lungs, which may increase the risk of pneumonia for the patient. The main benefit of saline instillation appears to be that it does stimulate a vigorous cough. This practice should be reserved for situations where patients do not cough adequately during suctioning. Saline is routinely instilled during bronchoscopy, when the patient's airway is anesthetized and coughing is minimal. More of the instilled solution can be recovered by suctioning through the bronchoscope.

Learning Hint

Have you ever experienced hard coughing or choking while you were drinking a fluid that accidentally entered your airway? That experience is similar to what patients experience when solutions are instilled into their airways.

FIGURE 6-4 A Nebulizer

A large-volume nebulizer, which can be connected via large bore tubing to a face mask, face tent, or tracheostomy mask to deliver aerosolized humidification



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6.2c Bland Solutions

Sterile and Distilled Water

Sterile water is free of microorganisms, but it may also contain additives to make it bacteriostatic. Distilled water is both sterile and pure (it has no additives, and all other constituents, such as naturally occurring minerals, are removed). Although any solution intended for inhalation must be sterile, water does not need to be distilled. In fact distilled water tends to be a bit more irritating than sterile water. Sterile water is commonly used as the diluent for other aerosolized medications, in humidifiers, in large-volume nebulizers, and in croup tents.

A cool mist of sterile water may have a soothing (humectant) effect on inflamed upper airways, as in croup, but there is little evidence that a significant amount of water deposits in the lower airways. It is also theorized that, because sterile water is hypotonic, it is more readily absorbed by mucus, and it may thin mucus more effectively than saline—but again, there is little objective evidence that either water or saline mixes well with mucus.

Devices that produce very dense aerosols tend to be more irritating to the airways. Dense aerosols are more likely to cause cough and even bronchospasm in susceptible individuals (such as asthmatics). However, the irritation and cough make these aerosols useful for sputum induction. It is a good idea to monitor the breath sounds of patients receiving aerosol treatments for sputum induction, because wheezing may indicate bronchospasm.

BVT Lab

Visit www.BVTLab.com to explore the student resources available for this chapter.

Normal Saline

Normal saline (0.9% sodium chloride) is physiologically normal. Because it is **isotonic** with body fluids (meaning that it has the same tonicity as other body fluids), it is less irritating and not as likely to cause bronchospasm as water. However, the administration of either normal or hypertonic saline to patients with COPD can cause a significant decline in lung function and should not be routinely recommended. It is frequently used as a diluent for other aerosolized medications, such as bronchodilators.

Hypertonic Saline

Hypertonic saline is any solution that contains more than 0.9% sodium chloride (NaCl). The most commonly available solutions contain 5% and 10% NaCl. These solutions are very irritating and are used only for sputum induction, particularly when the patient has a dry, nonproductive cough. Remember, the airway responds to irritation by producing more mucus.

Hypertonic saline solutions are more likely to cause bronchospasm than any of the other bland aerosols. Therefore it may be necessary to pretreat some patients with a bronchodilator. It is certainly advisable to monitor the patient throughout the treatment and be prepared to stop the treatment or administer a bronchodilator if necessary. As mentioned previously, hypertonic saline may cause a decrease in lung function in patients with COPD; however, it is beneficial in patients with cystic fibrosis because it aids in improving mucus clearance and subsequently lung function.

Hypotonic Saline

Saline is also available in a solution of 0.45%, or half-normal saline. Commercially available solutions for ultrasonic nebulizers are usually 0.45% strength. **Hypotonic** saline is less irritating than either sterile water or hypertonic saline. In addition to ultrasonic nebulizers, it can be used in any large-volume nebulizer or as the diluent for nebulized medications. Table 6-5 lists the common concentrations of saline.

TABLE 6-5 Common Concentrations of Saline

Percentage Solution	Solution Type
0.45%	Half-normal
0.9%	Normal
5%	Hypertonic
10%	Hypertonic

time for review

Why might hypertonic saline be better than sterile water or normal saline for sputum induction for a patient who has a dry, nonproductive cough?

6.3 MUCOLYTICS

6.3a Definition

When there is infection and/or dehydration of the pulmonary system, the gel layer of the mucus becomes thickened. Waste products of inflammation such as white blood cells (leukocytes), DNA, and other cellular debris add to the thickening of the mucus. Thick mucus cannot be mobilized by the action of the cilia, and when the cilia cannot keep the gel and sol layers in motion, the layers combine and a vicious cycle of thickening mucus ensues. In this situation humidity, mucolytic agents, and expectorants, or combinations of these agents, may be needed.

Mucolytics are drugs that control mucus by their direct action of altering the structure of the mucus molecule. In essence they facilitate expectoration of mucus by liquefying it. Mucolytics break down the complex molecular strands to thin the thick mucus. Two mucolytic agents are currently approved by the FDA for administration by aerosol to treat abnormal pulmonary secretions. They are acetylcysteine (Mucomyst®) and dornase alfa (Pulmozyme®). Investigation continues in this area, and new agents may be forthcoming.

Clinical pearl

Pioneer folk medicine recommended dissolving baking soda (sodium bicarbonate) in boiling water and breathing in the vapors to treat colds. Sodium bicarbonate is a weak base, and mucus becomes less adhesive in an alkaline environment. Increasing the pH of the mucus weakens the bonds of the polysaccharide chains. Alkalinization also activates proteases that are found in purulent sputum to help digest the excess protein molecules. There is also evidence that it potentiates the effects of acetylcysteine. However it has not been proven to improve mucus clearance, so its use cannot be recommended.

Acetylcysteine (Mucomyst®, Mucosol®)

Acetylcysteine is used to treat thick, viscous secretions, such as may be seen in cystic fibrosis, chronic bronchitis, tuberculosis, and acute tracheobronchitis. It acts by disrupting the disulfide bonds in the mucus. The long mucopolysaccharide strands are cross-connected with numerous bridges, including disulfide bonds. The long strands become a matted network of complex molecules. Breaking the disulfide bonds releases the mucopolysaccharide strands. The structure of the gel layer is broken down, and the viscosity and elasticity of the mucus is therefore reduced (see Figure 6-5). Since nebulized acetylcysteine can cause acute bronchospasm, it should be given after treatment with an inhaled beta-agonist, if it is used at all. Good bronchial hygiene therapies such as chest percussion, postural drainage, cough training, and positive expiratory pressure (PEP) therapy should be considered the first-line treatment. Oscillatory therapy combined with PEP therapy increases airway vibrations and facilitates secretion mobilization.

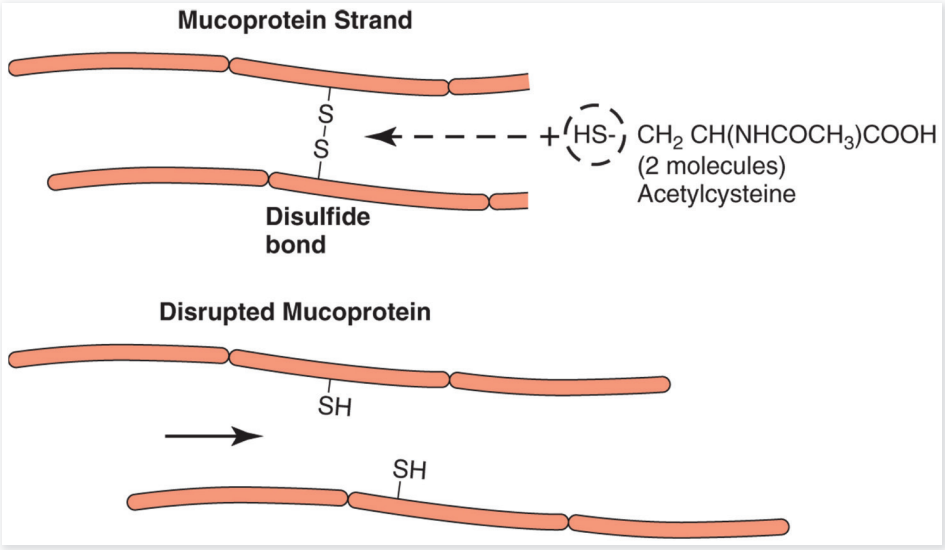
Dose and Administration Acetylcysteine can be given by aerosol or by direct instillation to the tracheobronchial tree. It is supplied in 10% and 20% solution strengths, and the dosages are as follows:

20% solution: 3 to 5 ml t.i.d. or q.i.d.

10% solution: 6 to 10 ml t.i.d. or q.i.d.

For instillation, 1 to 2 ml of either strength can be used.

FIGURE 6-5 Mucolytic Effects of Acetylcysteine (Mucomyst®)



When the 10% solution is used, the volume of the dose is 6 to 10 ml, which exceeds the optimal fill volume of most small-volume nebulizers. The dose will have to be divided, and the treatment time will therefore be very long.

Adverse Reactions Acetylcysteine is often poorly tolerated by patients because of its sulfurous odor and because its low pH (2.2) may cause bronchospasm, which may occur when the drug is administered by nebulization. Acetylcysteine is most likely to cause bronchospasm in patients with reactive airway disease, but bronchospasm can also occur in patients without any primary pulmonary disease. The 10% strength of acetylcysteine is less likely to cause bronchospasm than the 20% solution.

When acetylcysteine is to be nebulized, most clinicians opt to use the 20% solution in combination with a short-acting bronchodilator administered beforehand to prevent bronchospasm. It is better to administer the bronchodilator before the acetylcysteine, because even albuterol takes 15 minutes to onset of action and reaches its peak effect in 30 to 60 minutes.

Other complications of acetylcysteine include nausea, **rhinorrhea**, **bronchorrhea**, and **stomatitis**. *Rhinorrhea* and *stomatitis* are secondary consequences of irritation of mucous membranes. Excessive thin and watery secretions result. *Bronchorrhea* is the term used to describe excess thin, watery secretions in the airways. Rhinorrhea is what you would commonly call a runny nose.

Once a larger mucus molecule is broken down, it must be cleared, or mucus plugging can result. Deep breathing and coughing are essential to clear the mucus from the airways. Mucus plugging can occur in patients with ineffective cough or artificial airways. It is advisable to monitor patients carefully for changes in breath sounds or signs of respiratory distress. Suction equipment should be available for patients who cannot cough effectively.

Although it is flavorless, some patients object to the disagreeable odor caused by the release of hydrogen sulfide. Nausea and vomiting have been attributed to the smell. Acetylcysteine is corrosive to metal and irritating to mucous membranes, so patients should rinse their mouths and nebulizers (if they have metal parts) after treatments.

Other Uses Acetylcysteine is a potent antioxidant that is also used as an antidote in acetaminophen (Tylenol®) overdose. In this situation, acetylcysteine (Acetadote® is the brand name for the IV form) may be given orally or intravenously. If given orally, it may be mixed in cola or some other soft drink or, orange juice, or given by nasogastric tube. The package insert is a good reference for complete information on dosing, but we recommend calling a poison control center.

Clinical pearl

The hydrogen sulfide smell of acetylcysteine has been compared to that of rotten eggs, but it is actually flavorless. If the patient is to drink it, mixing it with cola makes it more palatable and reduces the risk of the patient vomiting.

Dornase Alfa (Pulmozyme®)

Dornase alfa is a clone of the natural human enzyme that digests extracellular DNA. Dornase alfa is a solution of recombinant human deoxyribonuclease (DNase). It received FDA approval in 1994.

Pulmonary secretions in cystic fibrosis are extremely thick and sticky because of abnormal chloride exchange mechanisms, which increase sodium and water absorption from the airway. This thickens airway mucus, impairs mucus clearance, and leads to infection. Because of their chronic pulmonary infections, cystic fibrosis patients have large numbers of neutrophils that congregate in the airways. As the neutrophils break down, a lot of their DNA is also left in the airways. This results in further thickening of the mucus.

Dornase alfa is indicated as **maintenance therapy** in the management of the viscous pulmonary secretions seen in cystic fibrosis. It is a proteolytic enzyme that breaks down the DNA material, decreasing the viscosity of the mucus and restoring its ability to flow. The change in sputum viscosity is dose-dependent—with higher doses producing thinner mucus.

Dose and Administration Dornase alfa is available in single-dose ampules containing 2.5 mg of drug in 2.5 ml of solution, administered once a day. Further analysis has suggested that patients older than 21 years of age with a forced vital capacity (FVC) greater than 85% of predicted may benefit from twice-a-day treatment. Dornase alfa should not be diluted or mixed with other medications. The solution should be refrigerated and protected from light. Medication that has been at room temperature for more than 24 hours or appears discolored should be discarded. The manufacturer recommends that dornase alfa should be nebulized only with the Hudson "T" Up-Draft II® disposable nebulizer, Marquest Acorn II® and Pulmo-Aide® compressor, PARI LC (reusable) Jet Plus® with PARI PRONEB® compressor, or the SideStream® Durable jet nebulizer with the MOBILAIRE™ or Porta-neb compressor, because these are the only ones that it has been tested with.

Clinical pearl

Under normal circumstances, the amount of sodium that the patient absorbs from the saline used as diluent for breathing treatments is so insignificant that it is not even considered. However in some patients, such as infants and adults who are on sodium-restricted diets, reducing sodium intake may be very critical. If breathing treatments are being given very frequently, it may be advisable to consider using sterile water as the diluent in order to avoid increasing the patient's sodium intake.

Adverse Effects Dornase alfa has been shown to be safe and well tolerated. Side effects are minimal but include voice alteration, pharyngitis, laryngitis, rash, chest pain, and conjunctivitis. It is contraindicated in patients with hypersensitivity to dornase alfa or to Chinese hamster ovary cell products (from which it is derived).

6.3b Expectorants

Expectorants increase the production and expectoration of mucus by increasing the amount of fluid in the respiratory tract and stimulating cough. They are one of the main ingredients in many OTC cough and cold medications. Expectorants are thought to work either by increasing vagal gastric reflex stimulation (parasympathomimetic) or by absorption into the respiratory glands to stimulate mucus production directly. Hypertonic saline, which was discussed earlier in this

chapter, is also considered to be an expectorant. Guaifenesin is one of the most commonly used expectorants. Other examples include terpin hydrate, ammonium chloride, and potassium iodide (see Table 6-6).

TABLE 6-6 Mucolytics and Expectorants

Drug	Trade Name	Adult Dosage
acetylcysteine	Mucomyst®	1–10 ml of 10%, or 2–20 ml of 20%, nebulized 3–4 times daily
dornase alfa	Pulmozyme®	2.5 mg daily via jet nebulizer
guaifenesin	Robitussin®	200–400 mg PO every 4 hours
potassium iodide	SSKI®	300–600 mg (0.3–0.6 ml), diluted in 240 ml fluid, PO 3–4 times daily

CONTROVERSY

There is some controversy about the effectiveness and use of expectorants. One problem is the difficulty of obtaining objective data to assess their effectiveness. The simplest and most frequently recommended method for preserving mucus clearance is still to drink plenty of water and other liquids that do not cause diuresis. Tea and alcohol should be avoided because of their diuretic effects. While maintaining hydration is frequently recommended, as previously discussed, there is little objective evidence that this strategy works to improve clinically important outcomes in diseases such as COPD.

6.3c Antitussives/Cough Suppressants

Stimulation of vagal sensory endings in the larynx, bronchi, or even the stomach can cause a cough. The cough that results from irritation of these nerve endings may not be contributing to clearance of the airways, as it may be dry and nonproductive. More coughing leads to more irritation of the nerve endings, and so on. It may be necessary to suppress this type of dry, hacking, nonproductive cough. Cough suppressants depress the cough center, which is thought to be located in the medulla. There are both narcotic and nonnarcotic preparations to choose from. Codeine is one of the common narcotic cough suppressants, and dextromethorphan is a nonnarcotic cough suppressant.

Cough suppressants should never be given to patients with thick retained secretions. They need to cough to clear them. You can also find combinations of drugs in OTC cold preparations, such as an antitussive and an expectorant. The rationale is that a frequent, dry, hacking cough is better replaced by a less frequent but more productive cough. However, the practice of combining an expectorant to stimulate mucus production with an antihistamine to dry secretions in OTC medications is questionable. The American College of Chest Physicians (ACCP) published evidenced-based clinical practice guidelines on cough suppressant therapy and concluded that antitussives can be useful in patients with chronic bronchitis but have little efficacy for cough due to upper-airway infection. Suppressant therapy is most effective when used for short-term decrease in coughing.

6.3d Conclusion

The mucociliary system preserves and protects the lungs from disease and dehydration. The normal structure and function of the mucociliary system should be maintained. When possible, avoid factors that contribute to excess mucus production, such as smoking, pollution, and allergens. When the integrity of the mucociliary system is compromised, therapy should be geared toward increasing mucus clearance and maintaining adequate hydration. This may be achieved through a variety of mechanisms, including:

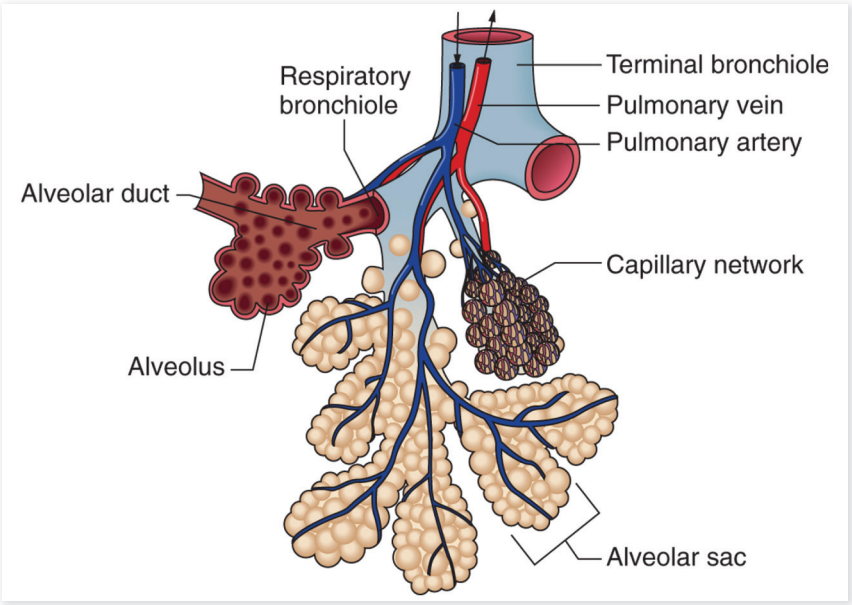
- Administration of bronchodilators
- Adequate systemic hydration
- Deep breathing and coughing
- Postural drainage
- Mucolytics
- Expectorants

6.4 SURFACE-ACTIVE AGENTS

6.4a Alveolar Physiology and Surfactant Synthesis

Throughout Chapter 5 and so far in Chapter 6, we have been discussing the anatomy and physiology of the conducting airways. We have also explored many of the pharmacologic agents that act on the airways themselves and the mucus they contain. Now we turn our attention to the area of the lungs beyond the terminal bronchioles, where gas exchange takes place. This is known as the *respiratory zone* of the lungs, and it includes the respiratory bronchioles, alveolar ducts, alveoli, and pulmonary capillaries (see Figure 6-6).

FIGURE 6-6 The Respiratory Zones of the Lung



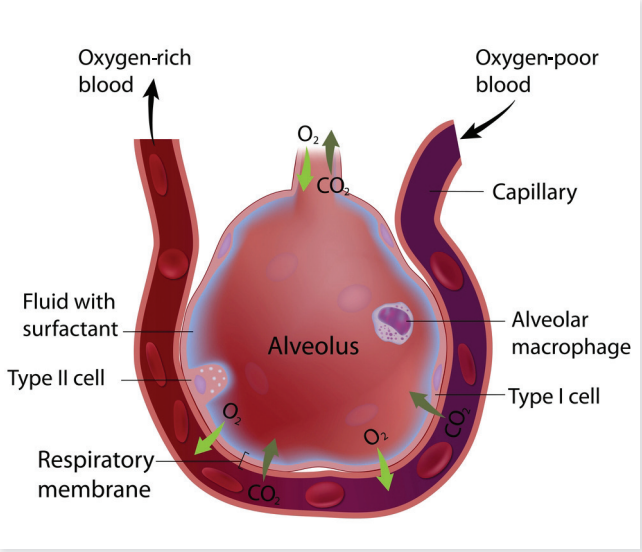
The walls of the respiratory bronchioles are made up of very thin, flattened squamous cells and a thin layer of connective tissue. They lack the smooth muscle and mucus-producing cells of the conducting airways. Alveolar ducts branch from the respiratory bronchioles, and the walls of the alveolar ducts are made up entirely of alveoli. Each alveolar duct ends in a cluster of alveoli, which together are called an alveolar sac. Each alveolar sac opens into about 10 to 16 alveoli.

The alveoli are made up of type I and type II pneumocytes. The type I pneumocytes are large, very thin, flat cells with tight junctions between them. Type I pneumocytes make up about 93% of the total alveolar surface area. They are ideally suited to allow for the diffusion of gases.

Type II pneumocytes are small, cuboidal cells found mainly in the corners between type I pneumocytes (see Figure 6-7). The type II pneumocytes manufacture a complex substance called **surfactant**. Surfactant consists of 80% phospholipids, 10% neutral lipids (cholesterol), and 10% surface proteins (SPs). The phospholipids are phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, and phosphatidylethanolamine. The surface proteins are SP-A, SP-B, SP-C, and SP-D. The theorized role of each of these proteins is listed in Table 6-7. Surface proteins B and C (SP-B and SP-C) appear to be critical to maintaining normal surfactant function, whereas SP-A and SP-D are not (see Table 6-7).

FIGURE 6-7 Structure of an Alveolus

Alveolar structure and cell types: Type I: squamous pneumocyte for diffusion; Type II: granular pneumocyte for surfactant production and cellular repair; Type III: alveolar macrophage for immune function



Source: Shutterstock

TABLE 6-7 Surfactant Proteins

Protein	Function
SP-A	Has host-defense properties; activates macrophage function; facilitates phagocytosis of pathogens
SP-B	Critical to surface tension–lowering property of surfactant
SP-C	Facilitates surfactant spreadability
SP-D	Functions as host-defense mechanism by binding to pathogens

Learning Hint

Try blowing up several balloons of different sizes. Note that some balloons require much more effort to blow up than others. This is because they have a higher surface tension. The balloon that is easiest to blow up has the lowest surface tension.

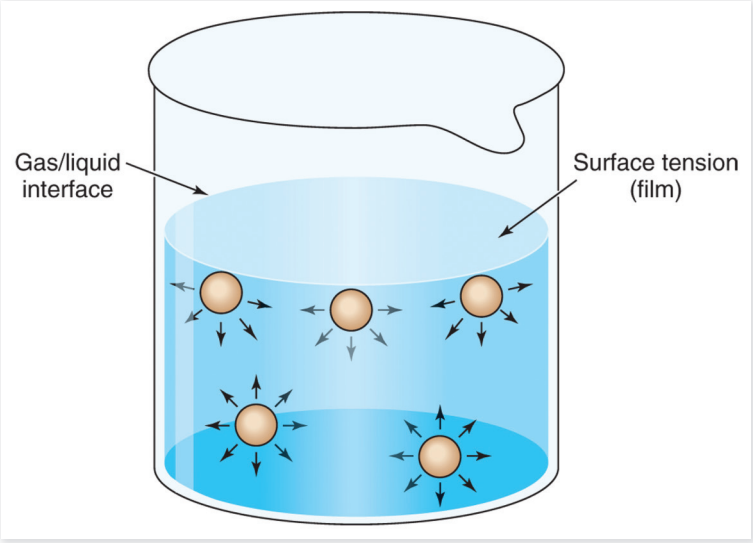
6.4b Surfactant Function

Surfactant is critical to maintaining the condition of the alveolar surface so that gas exchange can occur. Clinically, surfactant performs the following three functions:

- Prevents alveolar collapse
- Enables the lung to expand easily
- Prevents leakage of fluid from the alveolar capillary membranes

To understand the importance of surfactant, we must first understand surface tension. The surface of a liquid acts as if there were an elastic skin constantly pulling in, attempting to contract the liquid into the smallest surface area. This force is called **surface tension**. It is created by uneven forces of attraction on the molecules at the surface of the liquid. The molecules under the surface have equal forces of attraction all around them. The molecules at the surface are in contact with air (this is called the *gas–liquid interface*); there is no attraction between the surface molecules and air, so the surface molecules are pulled inward and down, creating the force called surface tension (see Figure 6-8). It is this surface tension that makes liquid contract into a small sphere, such as the water drops that "bead" on a freshly waxed car. Without surface tension, the water drop would spread out into a large puddle.

FIGURE 6-8 Surface Tension



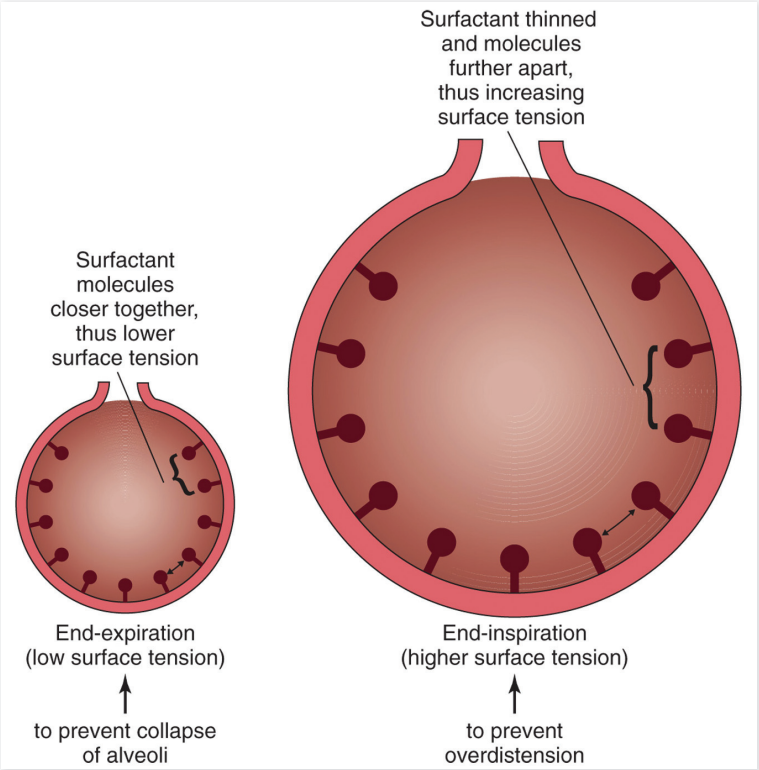
The surface of alveoli also has a layer of fluid, comprised largely of water. The greater the surface tension of the fluid, the smaller the sphere becomes; in turn, the smaller the sphere becomes, the greater the surface tension gets. By the law of LaPlace, the alveoli will eventually decrease to their critical volume. Below this volume, the force of the surface tension will cause the alveoli to collapse, resulting in atelectasis. Once alveoli collapse, the pressure required to reopen them is much greater than the pressure required to inflate an alveolus that is just above its critical volume. This pressure is called the critical pressure.

Surfactant is secreted by the type II pneumocytes and stored in vesicles called lamellar bodies. The lamellar bodies unravel in the alveoli, and the surfactant forms a thin film called a monolayer on the inner surface of the alveoli. The air–liquid interface is replaced with an air–lipid interface, which has a much lower surface tension. In this way the alveoli are stabilized above their critical volumes and do not collapse. Lower surface tension allows the alveoli to expand into a larger sphere, which provides a larger surface area for greater gas diffusion. The lower surface tension also makes it easier to inflate the alveoli, which results in a lower work of breathing.

How can the law of LaPlace be used to explain why a balloon can be very difficult to blow air into initially, but once started, blowing becomes easier?

The action of surfactant and its effect on surface tension is a very dynamic process. Surface tension varies with alveolar volume. On inspiration, the alveolar volume increases, spreading the surfactant molecules farther apart, and surface tension increases. This helps to prevent alveolar overdistension. On exhalation, the surfactant molecules are tightly packed, decreasing surface tension and preventing collapse (see Figure 6-9).

FIGURE 6-9 The Effects of Surfactant on Alveolar Surface Tension



Surfactant has a relatively short half-life and must be continuously replaced at the alveolar surface. During exhalation, old surfactant is squeezed out of the monolayer, and new surfactant is added on inspiration. Under normal circumstances most of the surfactant (90%–95%) is taken back up and recycled by the type II pneumocytes.

Because inflation and deflation are important in maintaining a healthy monolayer and low surface tension in the alveoli, you can see that lung collapse or atelectasis disrupts surfactant production. Hypoxia can also damage the type II pneumocytes and interrupt surfactant production, and repeated collapse and reopening of alveoli cause a lot of lung damage, inflammation, and leaking of protein-rich fluid into the alveoli. This also disrupts surfactant function.

time for review

Infants born prematurely may not have mature type II pneumocytes. What complications might ensue?

6.4c Indications for Surfactant Replacement Therapy

The major indication for surfactant replacement therapy is to prevent or treat respiratory distress syndrome (RDS) in infants. RDS is a disease associated mainly

with prematurity (less than 34 weeks' gestation) and low birth weight. The type II pneumocytes in these infants are not mature enough to produce surfactant. An inadequate amount of surfactant leads to alveolar collapse, hypoxemia, and increased work of breathing for the infant.

Surfactants have been used anecdotally and successfully to treat several other conditions, including:

- Meconium aspiration syndrome
- Full-term infants with RDS
- Pulmonary hemorrhage
- Congenital diaphragmatic hernia
- Severe pneumonia
- Any condition in which there is loss of surfactant and low lung volume

In these cases, the type II pneumocytes may have been damaged by perinatal asphyxia, or the surfactant may be deactivated by aspiration.

6.4d Types of Exogenous Surfactants

The surfactant that is produced naturally in lung tissue is called **endogenous surfactant**. **Exogenous surfactants** are produced outside the body and administered as a therapy. Two types of exogenous surfactants are currently available: natural/modified and synthetic. Synthetic surfactants are mixtures of synthetic components that are produced in the laboratory. This means that the drug is free of infection and foreign proteins, which is an advantage, but it may not perform as well as natural surfactant because of the organic chemicals that are substituted for the natural proteins.

Natural surfactant is obtained from animals by alveolar wash. The surfactant is then extracted from the liquid by centrifugation or simple filtration. The surfactant is modified by adding and removing certain components to improve its function in the lung, reduce protein contamination, and ensure sterility. This preparation consumes a lot of time, which adds to the cost of the drug. There is also a concern over the possibility of viral infection and immunologic reaction to foreign proteins. However, the advantage of natural surfactants is that they contain the phospholipids and proteins (SP-B and SP-C) necessary for absorption and spreading of the phospholipids.

Both natural and synthetic surfactants have been shown to be effective, but natural surfactants act more quickly and are associated with lower mortality, less barotrauma, and lower oxygen requirements. There were no significant differences in head-to-head trials of various natural surfactants.

6.4e Therapeutic Approaches

There are two therapeutic approaches to surfactant administration. In very premature infants (less than 30 weeks' gestation) there is a high probability that RDS will occur, so surfactant is given as soon as possible (usually within minutes) after birth. This is referred to as prophylactic treatment. Theoretically this strategy may prevent lung injury, but it is also associated with unnecessary treatment of some babies. Clinical trials suggest that prophylactic treatment compared to rescue treatment decreases morbidity and death in infants who are less than 30 weeks gestational age when they are delivered.

Rescue treatment is indicated for infants who demonstrate serious signs and symptoms of RDS. The advantage of rescue treatment is that only babies that really need it receive treatment, and there is more time to ensure good tube placement prior to administration of the surfactant. The down side of this approach is that it may allow for the progression of lung injury.

6.4f Representative Drugs

Calfactant (Infasurf®)

Calfactant is a natural surfactant.

Dose and Administration Calfactant is supplied as a refrigerated suspension that does not have to be warmed to room temperature before use. The dose is 3 ml/kg of body weight administered intratracheally every 12 hours. Three doses is the maximum.

Beractant (Survanta®)

Beractant is a natural/modified surfactant comprised of natural bovine (cow) lung extract modified with three other additives.

Dose and Administration The dose is 4 ml/kg of birth weight administered by direct tracheal instillation. The dose can be repeated in 6 hours for up to 4 doses if required on the basis of clinical judgment.

Poractant Alfa (Curosurf®)

Poractant alfa is a natural porcine surfactant that must be kept refrigerated prior to use.

Dose and Administration The initial dose is 2.5 ml/kg birth weight. This may be followed by up to two additional doses of 1.25 ml/kg birth weight at 12-hour intervals.

Lucinactant (Surfaxin®)

Lucinactant is a synthetic surfactant that also requires refrigeration prior to use. As discussed above, natural surfactants are favored over synthetic surfactants such as lucinactant due to improved clinical outcomes with natural surfactants.

Dose and Administration 5.8 ml/kg birth weight should be administered through the endotracheal tube up to a total of four doses within the first 48 hours of life.

6.4g General Techniques of Surfactant Administration

All forms of surfactant are administered intratracheally. This requires placement of an endotracheal tube. The tube must be positioned properly above the carina to ensure even distribution to both lungs. The baby should be suctioned before administration of surfactant to remove any secretions that would interfere with medication delivery. Specific brands may call for modifications to the general guidelines for surfactant administration.

The surfactant should be allowed to come to room temperature. The calculated dose is drawn into a syringe. The intubated baby is placed on his or her side. The dose is divided into four **aliquots**, or equally divided portions; two aliquots are administered with the baby turned to the right side and two aliquots are administered with the baby turned to the left side. This procedure is intended to distribute the surfactant as widely as possible throughout the lung. However there is no real evidence to support this practice. There are three methods for instilling surfactant into the endotracheal tube:

Sideport Adapter

The solution is instilled down the baby's endotracheal tube through the sideport of a special adapter on the endotracheal tube. This technique allows the medication to be instilled while the infant is attached to the ventilator. However reflux of the solution may occur (see Figure 6-10a).

Catheter

The baby is briefly disconnected from the ventilator while a 5-French catheter is placed directly in the endotracheal tube to instill the surfactant. The catheter is withdrawn and the infant is returned to the ventilator after each instillation.

Double-Lumen Endotracheal Tube

This endotracheal tube has a catheter embedded into the wall of the tube to provide distal instillation like a catheter, while the baby remains attached to the ventilator as with the sideport adapter (see Figure 6-10b).

6.4h Adverse Reactions

Babies must be monitored closely following surfactant administration because there may be rapid improvements in lung compliance. As the lung compliance increases, tidal volumes may increase significantly. Ventilator pressure will need to be decreased to prevent alveolar damage or rupture. Oxygen levels in the baby's blood may also increase rapidly, so the oxygen concentration will also need to be decreased. Monitoring may include breath sounds, chest radiographs, chest movement or tidal volume changes, arterial blood gases, and oxygen saturation measurements. The hazards can be divided into those that occur during administration and those that occur after administration.

Clinical pearl

The transient decrease in oxygen is due to the initial diffusion barrier of the drug. This is very transient and should not be significant, especially with proper preoxygenation. The bradycardia and/or hypotension may be secondary to hypoxemia or may be a result of vagal stimulation.

During Administration:

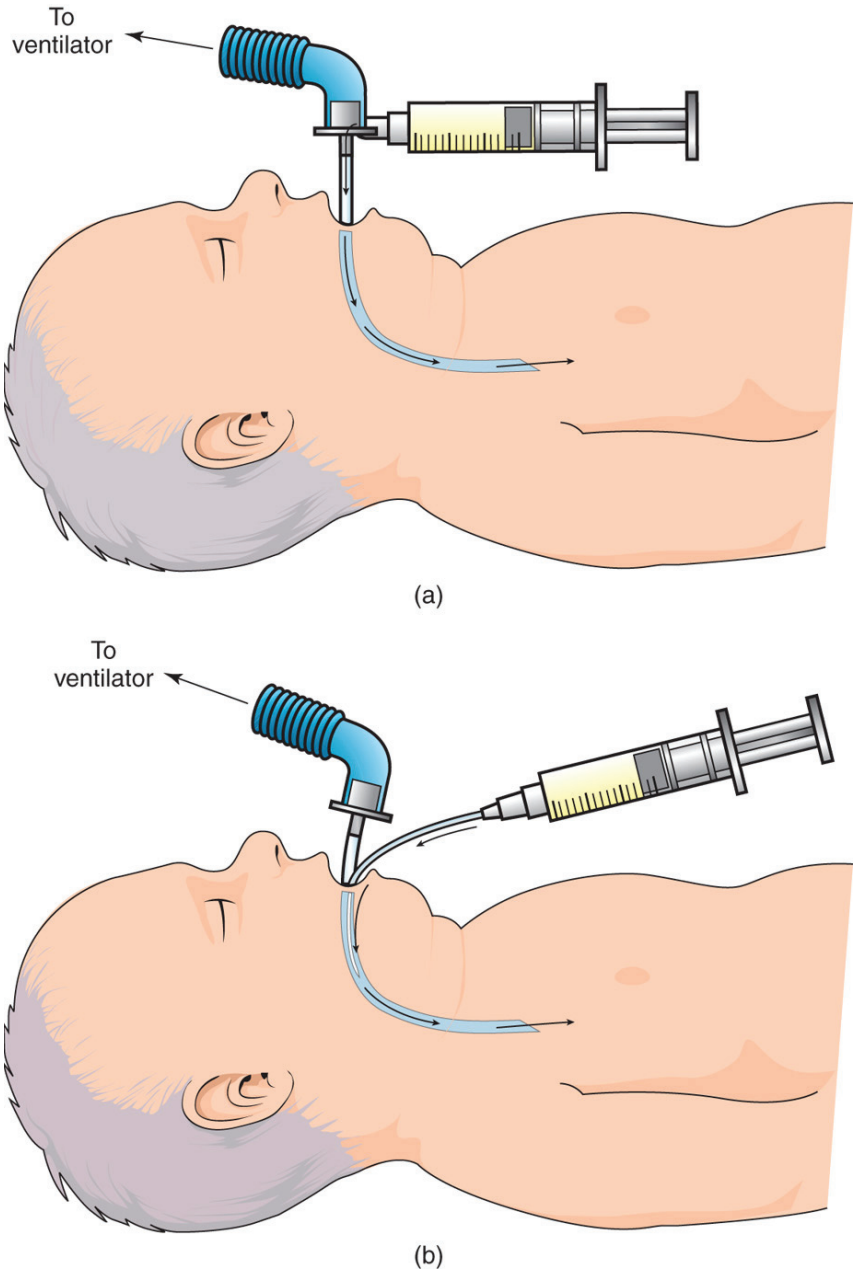
- Reflux of solution
- Transient decrease in oxygenation
- Bradycardia and/or hypotension

After Administration:

- Hyperoxygenation
- Hyperventilation (decrease in $PaCO_2$)
- Patent ductus arteriosis (PDA)

FIGURE 6-10 Surfactant Administration Techniques: (a) Sideport Adapter; (b) Double-Lumen Endotracheal Tube

Note: The baby is pictured on his/her back, but should be turned side-to-side during administration.



Uncommon Side Effects:

- Apnea
- Pulmonary hemorrhage

6.4i Surfactant Administration in Adult Patients

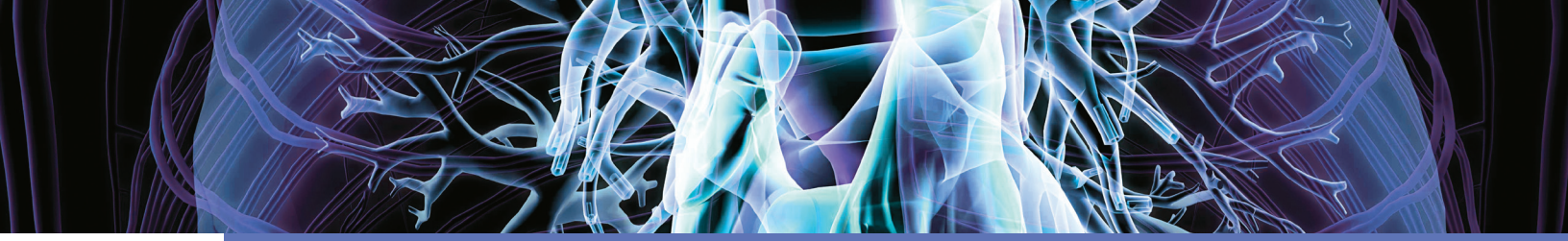
So far surfactant has not been proven to be successful in treatment of adults and children with acute RDS (ARDS). Only a few studies of adults with ARDS have been done, and the results have been conflicting. There are differences in the pathophysiology of ARDS. In RDS of the newborn, the problem is a primary surfactant production deficiency, whereas in ARDS, the surfactant deficiency is secondary to lung injury and inflammatory response. This may account for the different responses to surfactant replacement therapy. Beractant, poractant alfa, and calfactant are available in the United States, and several other surfactants are available throughout the world. See Table 6-8 for the commercially available surfactants.

TABLE 6-8 Commercially Available Surfactants in the United States

Generic Name	Trade Name	Type	Dose
beractant	Survanta®	Natural/modified	4 ml/kg
calfactant	Infasurf®	Natural/modified	3 ml/kg
poractant alfa	Curosurf®	Natural/modified	2.5 ml/kg
lucinactant	Surfaxin®	Synthetic	5.8 ml/kg

LIFE SPAN CONSIDERATIONS

Respiratory distress syndrome (RDS) in children is nearly always found in infants born prematurely. Acute respiratory distress syndrome (ARDS) can be found in both children and adults and is generally due to a severe illness that affects the lungs by damaging the alveoli. Unfortunately the similarity of these terms can cause confusion for health-care professionals *but* not for readers of this text.



Summary

Proper function of the mucociliary system is critical to maintain proper pulmonary hygiene. Bland aerosols can deliver high levels of humidity to assist proper function. In addition mucolytic drugs can be administered to thin mucus to facilitate expectoration of thickened secretions that occur in many pulmonary disease conditions. Expectorants and antitussive agents can also assist in helping to treat pulmonary irritation and secretion problems.

Proper functioning of surfactant at the alveolar level is needed to maintain proper surface tension to prevent both collapse and overdistension of the alveoli. Exogenous surfactant replacement therapy can prevent or treat premature or low-birth-weight infants with respiratory distress syndrome (RDS).

REVIEW QUESTIONS

1. What layer(s) make up the mucosal blanket that covers the airways?
   (a) sol
   (b) gel
   (c) (a) and (b)
   (d) none of the above

2. Bland aerosols are aerosols that
   (a) have no taste
   (b) are boring
   (c) are colored
   (d) are nonmedicated

3. A patient with a dry, nonproductive cough who requires a sputum induction for tuberculosis testing may benefit most from what solution?
   (a) hypertonic
   (b) hypotonic
   (c) sterile water
   (d) isotonic

4. The drug dornase alfa (Pulmozyme®)
   I. is indicated for maintenance therapy for secretions in cystic fibrosis patients
   II. ruptures disulfide bonds in sputum
   III. should not be mixed with other medications
   IV. should be refrigerated and protected from light

   (a) I, II, and III
   (b) I, III, and IV
   (c) I and IV
   (d) IV only

5. During surfactant replacement administration, the patient should be monitored for what hazards or conditions?
   I. improved lung compliance
   II. transient decrease in oxygenation
   III. reflux of solution
   IV. bradycardia

   (a) I, II, III, and IV
   (b) I and II
   (c) I and III
   (d) II, III, and IV

6. State four functions of mucus in maintaining a healthy pulmonary system.

7. What is the typical dose range for acetylcysteine, and how can it be delivered?

8. Which of the following would be best to prevent bronchospasm in a patient who is ordered nebulized acetylcysteine?
   (a) Administer 2 puffs of salmeterol before the acetylcysteine.
   (b) Add 2.5 mg of albuterol to the acetylcysteine.
   (c) Administer 2.5 mg of albuterol after the acetylcysteine.
   (d) Pretreat the patient with 2.5 mg of albuterol by nebulizer 20 minutes prior to the acetylcysteine.

9. You are preparing to administer beractant to an 800-g male with RDS. Which of the following is the appropriate dose?
   (a) 4 ml
   (b) 3.2 ml
   (c) 5 ml
   (d) 2 ml

10. Critical functions of surfactant in the lung are that it
    I. improves oxygenation
    II. prevents alveolar collapse (atelectasis)
    III. reduces the risk of intrapulmonary hemorrhage
    IV. decreases the work of breathing

    (a) I only
    (b) I and II
    (c) I, II, and IV
    (d) I, II, III, and IV

11. What is the primary indication for surfactant replacement therapy?
    (a) pneumonia
    (b) meconium aspiration
    (c) respiratory distress syndrome (RDS)
    (d) pulmonary hemorrhage

12. How is surfactant administered?
    (a) by MDI
    (b) by instilling the solution directly into the endotracheal tube
    (c) by aerosol
    (d) intravenously

13. Calfactant is ordered for a baby weighing 1.5 kg. What dose should be given?
    (a) 4.5 ml
    (b) 6.0 ml
    (c) 3.75 ml
    (d) 7.5 ml

Case Study 1

A COPD patient

A COPD patient is admitted with pneumonia. He is not able to produce his usual amount of sputum. The patient states that when he does cough up sputum, it is very thick and yellow. Upon auscultation, you note that he has expiratory rhonchi bilaterally and crackles over the right middle and lower lobes. He is already receiving aerosol treatments with albuterol and ipratropium bromide. He is also on antibiotics.

(a) What other medication may help to reduce the viscosity of this patient's sputum?
(b) What other therapies and recommendations do you have for this patient?
(c) What would you tell this patient concerning systemic hydration?

Case Study 2

A baby boy

A baby boy is born at 29 weeks' gestation. He weighs 2 kg. He is admitted to the neonatal intensive care unit with respiratory distress, nasal flaring, and grunting. His oxygen requirement has increased to 70%.

(a) What pathologic process should be suspected?
(b) What medication is indicated, and when and how should it be given?
(c) Would this be considered prophylactic or rescue therapy?
(d) What patient parameters should be monitored before and after medication administration?