

# COPD with a Focus on the Epidemiology, Pathophysiology, and Treatment Options

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This accredited program is targeted **nurses** and **pharmacists** practicing in hospital and community pharmacies. Estimated time to complete this monograph and posttest is 60 minutes.

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## Program Overview:

To provide nurses and pharmacists with an understanding of COPD treatment options as well as its epidemiology and pathophysiology.

## OBJECTIVES:

After completing this program, participants will be able to:

- Describe the etiology and epidemiology of chronic bronchitis and emphysema in the United States, and worldwide.
- Describe the differences in the mechanism of action between *β2 adrenergic agonists, methylxanthine, anticholinergic agents* and leukotriene modifiers.
- Describe the benefits of long-acting bronchodilators, short-acting bronchodilators, *short acting anticholinergic bronchodilator, long acting anticholinergic bronchodilator* in COPD management.
- Identify the role of antimicrobial therapies in the management of *acute exacerbations of chronic bronchitis and emphysema*.

# **COPD with a focus on the epidemiology, pathophysiology and treatment options.**

Promise Onuorah

## **Introduction**

COPD is an obstructive pulmonary disease characterized by progressive resistance to airflow. Cigarette smoking is the greatest risk factor for developing COPD world wide, followed by occupational dust, chemicals, and indoor air pollution. Emphysema and chronic bronchitis are the two most common conditions comprising COPD. Individuals who smoke cigarettes typically exhibit symptoms of both emphysema and chronic bronchitis, or specifically, chronic inflammation that leads to parenchymal destruction. Destruction and damage to the integrity of the parenchymal structures upon exposure to noxious particles and gases lead to airway obstruction in the individual. 1, 2, 3

Chronic bronchitis is defined by its clinical manifestation as opposed to its pathogenesis. It is characterized by chronic or excessive secretion of mucus into the bronchial tree, resulting in a persistent or chronic cough. On the other hand, emphysema is defined in terms of its pathology, or specifically, damage to the respiratory unit. Emphysema is characterized by destruction of the bronchial walls, and enlargement of the air spaces distal to the terminal bronchioles. Emphysema is also characterized by a decrease in the surface area of the alveolar and capillary bed, both of which are essential for gas exchange in the lungs. Dyspnea and hypoxia are potential ramifications of a decrease in the rate of diffusion of carbon dioxide and oxygen in the lungs. Destruction of the terminal bronchioles also causes a loss of elasticity in the surrounding tissue and consequently, a loss of recoil tension during expiration. 1, 2, 3

## **Epidemiology**

Chronic bronchitis and emphysema typically co-exist in COPD, thus epidemiology data considers both conditions under COPD. COPD is the fourth leading cause of death in the United States with a reported 124,477 deaths in 2007. In 2008, an estimated 13.1 million American adults were diagnosed with COPD, however, the true prevalence of COPD in the United States may be greater than 24 million American adults. Of the 13.1 million Americans diagnosed with

COPD, 9.8 million individuals were diagnosed with chronic bronchitis and the remaining 25% were diagnosed with emphysema. 2, 4

In recent years, COPD related symptoms have been the cause of 700,000 hospitalizations, 15 million hospital visits, and 1.5 million emergency room visits. In addition to the medical, emotional and physical burden of COPD, the financial impact of this chronic disease continues to climb. The financial burden of COPD was estimated at \$49.9 billion in 2010, and by the year 2020, COPD will become the fifth most financially burdensome disease in the United States. 2, 4

## **Etiology**

Risk factors for developing COPD can be divided into environmental factors and host factors. Cigarette smoking remains the principle cause of asthma in 90 percent of patients with emphysema and chronic bronchitis, and current smokers are 12 to 13 times more likely to die from COPD complication. Total number of cigarettes smoked per year, the age which one started smoking, and the individual's current smoking status are predictive measures of COPD mortality. 5 It is important to note that only 15 to 20 percent of smokers develop COPD, thus there must be environmental and genetic factors that increase one's susceptibility to developing COPD. 2

Exposure to environmental allergens and occupational particles are important risk factors for COPD. When substances such as silica dust, grain dust, asbestos, diisocyanate, mineral dust, and organic dust are inhaled, it causes inflammation of the lung tissue and cellular damage. Research studies also found a direct link between COPD and occupations such as welding, rubber and plastic manufacturing, coal mining, and brick making. A person who smokes cigarettes and works in a textile factory or a coal mine inhales a greater number of particles and has an increased risk of developing COPD. 2, 6

Although environmental and occupational substances increase an individual's risk for developing COPD, ongoing studies of the role of genes in the development of COPD have found a direct link between Alpha 1 antitrypsin and emphysema. Alpha 1 antitrypsin is a protein produced in the liver. The primary function of this protein is to protect lung cells from elastase released by neutrophils. Mutations in this gene result in several types of alpha 1 antitrypsin deficiency, and a decrease in the production of this enzyme. Alpha 1 antitrypsin associated

emphysema is a genetic disorder inherited in an autosomal recessive pattern, and is responsible for two to three percent of emphysema cases in the United States. 2, 7, 8, 9, 10

Other host factors that increase an individual's susceptibility to developing COPD are lung growth and airway hyper responsiveness. Individuals that are hypersensitive or hyper-responsive to inhaled particles incur a significant amount of cellular and tissue damage, and as a result, lung function declines. Additionally, individuals who were born prematurely, had low birth weight, or impaired lung growth during gestation, have an increased risk of developing COPD, especially if they have respiratory infections during childhood. 2-3

## **Pathogenesis**

### *Pathogenic mechanisms of COPD*

COPD is characterized by chronic inflammation which leads to chronic airflow limitation and widespread damage to the pulmonary vasculature, lung parenchyma, and small and large airways. Exposure to tobacco smoke, or provocative particles and gas, induce the migration and infiltration of pro-inflammatory cells, primarily neutrophils, CD8+ T cells, and macrophages to the lungs. These pro-inflammatory cells release chemical mediators including interleukin 8, leukotriene B4, and TNF-A to the extracellular environment to perpetuate the inflammation. 1, 2, 11-13

### *Chronic Bronchitis*

Cigarette smoke is the leading cause of chronic bronchitis. Cigarettes contain reactive oxygen species, thousands of compounds, and tar that causes inflammation of the lungs. These compounds, as well as other inhaled particles and gases, induce the innate and adaptive immune response. As neutrophils and macrophages infiltrate the airway lumen and wall, bronchial epithelial cells synthesize and release interleukin 8 (IL-8). IL-8 is a strong chemo attractant and a significant mediator in chronic bronchitis. It perpetuates the inflammatory response by activating and attracting lymphocytes, and neutrophils to the parenchymal cells in the bronchi. The influx of immune cells to the airways, lungs, and alveolar is believed to be responsible for the initiation and maintenance of mucus accumulation, and cough patients with chronic bronchitis. 2, 11-13

The clinical manifestations of chronic bronchitis are attributed to airway narrowing, damage to the epithelial cells in the airways, and scar tissue formation. Activation and infiltration of neutrophils, macrophages, lymphocytes, and leukocytes to the airways cause hypertrophy of the airway mucus glands. An increase in the number and size of goblet or mucus producing cells leads to mucus hyper secretion and obstruction of the bronchial lumen. 2, 12-14

Chronic airway inflammation results in damage to the epithelial cells lining the airways, and the airway denudation. The cilia bronchial epithelium layer is also damaged, and normal mucociliary clearance is severely impaired or completely abolished. The extensive damage to the epithelial cells results in a repair process which eventually leads to scarring, fibrosis, and replacement of the columnar epithelium with a patchy squamous metaplasia. Peribronchial fibrosis and increased proliferation of bronchial smooth muscle cells are prominent features of chronic bronchitis. Hyper-responsiveness to non-specific stimuli such as histamine is also seen in patients. 2, 11-13

Destruction of ciliary cells in the epithelial layer of the airway enables viral organisms to colonize the airways, resulting in acute respiratory tract infections. Lower respiratory tract pathogens including influenza virus and adenovirus, as well as common cold viruses such as rhinovirus and coronavirus account for the majority of infectious agents associated with acute bronchitis. Human metapneumovirus, parainfluenza virus, and bocavirus are respiratory viral pathogens found in patients with acute bronchitis. In addition, *C. pneumoniae*, *M. pneumoniae*, and *B. pertussis* are also associated with respiratory tract infections in chronic bronchitis patients. 55

#### *Clinical Manifestations of Chronic Bronchitis*

Chronic inflammation of the airways, increased proliferation of mucus glands, and hyper-secretion of mucus causes lumen narrowing, and airway obstruction. The increased amounts of mucus produced in chronic bronchitis patients causes a thick, productive cough composed of large amounts of mucus, damaged cells, and free DNA from lysed and damaged epithelial cells. Chronic airway injury, lumen narrowing, and airway obstruction from increased amounts of mucus cause wheezing in patients. The secreted mucus also contains immune cells, epithelial

cells, and possibly bacterial organisms, that make the mucus highly viscous, and further impairs breathing.12-16

As the disease progresses the cilia that lines the bronchioles become damaged. In some cases, cilia in the bronchioles are completely destroyed and are unable to remove the excess amounts of mucus produced by goblet cells. Excessive amounts of mucus accumulate and clog the airways, forcing the individual to cough to remove the accumulated mucus. The cough is typically worse in the morning since mucus continues to accumulate while the individual sleeps. In addition to increased coughing, the individual experiences coarse crackles that can be heard during inhalation and exhalation. 12-16

A decrease in the oxygen content of the blood is another consequence of airway obstruction. To combat this, the individual hyperventilates and takes deep breathes in an attempt to deliver more oxygen to the cells, and expel carbon dioxide from the body. The constant hyperventilation eventually increases the lung volume, and the diaphragm becomes compressed. The heart rate increases, and the individual may experience an elevation in pulmonary artery pressure, or pulmonary hypertension. The heart may also increase in size, and large pulmonary arteries is common in patients with chronic bronchitis.12-16

Airway obstruction and narrowing can also increase the expiratory reserve volume. An increase in the respiratory reserve volume is a strong indicator that air is trapped in the lungs as a result of early closure of the airways and obstruction. Another consequence of chronic bronchitis and lumen obstruction is respiratory acidosis as carbon dioxide levels rise in the blood. 12-16

### *Emphysema*

Emphysema is characterized by progressive destruction of lung parenchyma, enlargement of distal air spaces, destruction of the alveolar capillary bed, and destruction of the elastic connective tissue which supports the structures of the lung. Destruction of the airway walls causes enlargement of the airspace, while loss of the alveolar capillary bed decreases the diffusion capacity of oxygen, eventually leading to hypoxemia. Loss of the alveolar wall also impairs the lung's ability to remove excess amounts of carbon dioxide in the body. It results in increased respiration and in some cases, respiratory acidosis. Alveolar destruction and

enlargement of the distal air spaces is characteristic of centriacinar and centriobular emphysema.  
11-16

Oxidants from cigarette smoke or super-oxide anions cause a protease-anti protease imbalance. These proteases target proteolytic enzymes, inhibit the protective activity of protease inhibitors, and eventually lead to tissue destruction. The primary mechanism of disease pathogenesis is the breakdown of connective tissue components, primarily elastin. Oxygen reactive species, primarily from cigarette smoke, cause the mobilization and infiltration of neutrophils and macrophages to the lungs. Neutrophils secrete elastase, a protein which inactivates alpha-1 protease inhibitor, and causes the destruction and loss of elasticity in the lung parenchyma and elastic connective tissue. The loss of elastic connective tissue diminishes the elastic recoil in the lungs, and consequently, reduces the maximal expiratory airflow. Lung compliance is significantly increased, meaning the lung is easily distended, however, it empties slowly. The lungs become chronically hyper-inflated, which eventually leads to expiratory collapse of the airways. 11-13, 17

Alpha1-antitrypsin deficiency is an inherited disorder that significantly increases an individual's risk for developing emphysema. Interleukin-6 induces the synthesis and elevation of serum alpha1-antitrypsin, an acute phase reactant protein produced by the liver. Alpha1-antitrypsin inhibits protease enzymes such as elastase. Elastase is released in the extracellular environment by neutrophils during an acute inflammation to destroy foreign proteins in the lungs. Alpha1-antitrypsin deficiency is characterized by chronic tissue breakdown, primarily lung tissue, as well as extremely low levels of this anti-protease. The absence of this protein allows elastase to destroy elastin and the alveolar walls, resulting in enlargement of the alveolar and airways, in addition to fibrosis. 11-13, 18

#### *Clinical Manifestations of Emphysema*

Destruction of alveolar capillary beds and lung parenchyma increases the individual's susceptibility to hypoxemia. The loss of capillaries, alveolar, and tissues that form a barrier between air and blood results in areas of increased ventilation, in relation to perfusion. Oxygen saturation of hemoglobin decreases and serum levels of carbon dioxide increases. As carbon

dioxide increases in the blood, they also displace oxygen molecules from heme molecules. The individual begins to hyperventilate in an attempt to counteract this, and breath sounds such as crackles and wheezing are observed. Another consequence of increased levels of carbon dioxide in the blood is respiratory and metabolic acidosis. 12-13

Hyperinflation of the lungs, and depression of the hemidiaphragms is commonly observed in emphysema patients. Loss of elastic recoil in the lungs decreases the maximal respiratory airflow. It also causes the airway to close prematurely, and air becomes trapped in the lung. Trapped air causes an increase in the residual lung volume as well as the total lung capacity, and residual volume. 12-13

A significant number of patients with emphysema incur an extensive amount of damage to the vessels in the lungs and airway. In severe cases, the pulmonary valve may close completely resulting in pulmonary hypertension. The right side of the heart works and beats faster than normal to pump deoxygenated blood to the lungs, and overcome the resistance to flow. Right heart failure may occur in the worst cases, followed by peripheral edema. 12-13

## **Routes of Drug delivery to the Lungs**

### *Inhaled Route*

Aerosol delivery of drugs through inhalation is the preferred method of treating COPD. Inhaled therapeutic agents are site specific, induce a direct effect on the airways, and increase the therapeutic ratio. Drugs for COPD may also be administered by parenteral or oral routes. Inhalation is the preferred route of delivery for  $\beta$ 2-agonists, anticholinergics, and corticosteroids. Small doses of  $\beta$ 2-agonists and anticholinergics immediately induce bronchial smooth muscle dilation, while inhaled corticosteroids have a long time period before the onset of action. 2, 19-20

Pressurized metered-dose inhalers, space chambers, dry powder inhalers, and nebulizers are the devices commonly used to deliver inhaled drugs. The inspiratory flow rate is the most important patient factor in determining particle deposition. Inhaled particles are absorbed in the lumen of the airway where they target the cells involved in chronic inflammation. When these

drugs are absorbed in the airways, they enter bronchial circulation and are further dispersed to peripheral airways. The size of the inhaled particles is the most important factor in determining the site of aerosol deposition in the respiratory tract. Larger particles deposit in the upper airways and are more likely to be retained in the airways, while smaller particles are suspended and exhaled as a gas. Smaller particles are more likely to be distributed via pulmonary circulation, which in turn increases the likelihood that the drug will be deposited in the alveolar and absorbed from the lungs. Particles between 2 to 5 microns settle in the small airways, and thus are the optimum particle size for treating COPD. 2, 19

Metered-dose inhalers MDIs contain a metering valve, and between 100 to 400 doses of the active drug. The drug is either suspended in micronized powder or in solution, and is propelled out of the MDI with the aid of a vapor-pressure propellant such as hydrofluoroalkane. When actuated, MDIs are able to deliver 5 to 50 percent of the actuated dose, and the optimal inspiratory flow is deep and slow. Spacer chambers are frequently used with pressurized metered-dose inhalers to enhance lung delivery, and reduce oropharyngeal deposition. Spacer devices are different from MDIs in that the liquid propellant is evaporated prior to inhalation. Evaporation of the liquid propellant decreases the size and speed of particles that enter the upper airways. Large particles deposit in the oropharynx, thus reducing the size of the particles increases the proportion of the active ingredient that enters the lower airways. This is especially important for inhaled corticosteroids since oropharyngeal deposition results in adverse local reactions. 2, 19

Dry micronized powders are breath actuated and deliver about 10 to 30 percent of the drug. A higher inspiratory flow rate is required to increase the amount of the active ingredient deposited in the larger airways, since air turbulence allows the drug to be delivered as a powder. The patient should be advised not to exhale into the inhaler as it moistens the powder, thereby causing it to aggregate into larger particles that deposit in the oropharynx. 2, 19

A jet nebulizer and an ultrasonic nebulizer are two basic types of nebulizers. Jet nebulizers contain the drug in the liquid state, which is actuated during tidal breathing. When the drug is actuated, a stream of oxygen moves from the bottom of the tube up through the liquid, creating a droplet cloud that is deposited in the airways. An ultrasonic nebulizer uses a vibrating,

high-frequency electricity to deliver the active ingredient. Nebulizers typically deliver 5 to 15 percent of the starting dose, and thus can be used in treating acute COPD exacerbations. 2, 19

### *Oral Route*

Drugs for treating COPD may also be administered orally. Orally administered therapeutic agents require higher doses than those inhaled, thus systemic side effects are common. The increased risk of systemic adverse effects causes inhaled drugs to be preferred over orally administered drugs for the treatment of COPD. It is important to note that drugs such as theophylline are only effective when administered orally, while corticosteroids may be administered orally or via inhalation.2, 19

### *Parenteral Route*

Drugs for COPD may be administered intravenously for severely ill patients. Parenteral administration of drugs increase the risk of systemic side effects, since there are higher concentrations of the drug present in the blood. 2, 19

## **COPD Treatment options**

### *Nonpharmacologic Therapy*

Smoking cigarettes is the greatest risk factor for developing COPD, thereby smoking cessation is the most important factor in preventing and stopping the progression of COPD. Exposure to cigarette smoke and noxious particles results in chronic cough and sputum production, shortness of breath, hyperinflation of the lungs, loss of elastic connective tissue, abnormal gas exchange, decreased maximal ventilation, and pulmonary hypertension. While COPD is treatable, early intervention and detection can prevent the progression of disease. Smoking cessation at any point in one's life greatly prevents and slows the progression of disease. Studies of patients with mild to moderate COPD have shown that reduced exposure or avoidance of cigarette smoke improves lung function, especially the forced expiratory volume in one second (FEV1), reduces mortality, and reduces the symptoms of COPD, such as wheezing and coughing. 21-27

Nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine patches, varenicline, and bupropion are the first line of therapeutic agents used to help with smoking cessation. The duration period for agents are typically between eight to 12 weeks, however, some individuals require a longer time period. Studies have shown that bupropion, an antidepressant that inhibits the re-uptake of serotonin, dopamine, and noradrenaline, doubles the cessation rate when used in conjunction with behavioral support. The smoking cessation rate with bupropion is further increased when a nicotine patch is also used. Nortriptyline is a tricyclic antidepressant shown to be effective in smoking cessation therapy. Imipramine, doxepin, venlafaxine, fluoxetine, and moclobemide are antidepressants shown to be effective in smoking cessation. Other pharmacotherapies effective in smoking cessation and reducing withdrawal symptoms include clonidine, an  $\alpha$  noradrenergic agonist, as well as varenicline, and mecamylamine, both of which are nicotine agonist. 27-30

Respiratory infections such as influenza are commonly observed in COPD patients. Respiratory infections exacerbate the underlying disease state, and in some cases, may lead to respiratory failure, thus, annual vaccinations are highly recommended for patients with COPD. Influenza vaccination reduces disease complications and risk of death by 50% in COPD patients. Hypoxemia is another consequence of airway obstruction, and destruction of the alveolar capillary bed. Supplemental oxygen therapy is highly recommended for patients with COPD and chronic hypoxemia. Continuous oxygen therapy have been shown to significantly decrease the mortality rate, decrease pulmonary vascular resistance, increase the survival rate, and improve the overall quality of life in patients with COPD. Oxygen supplementation by be delivered via an oxygen concentrator such as a nasal cannula or face mask, in a liquid reservoir, or compressed into a cylinder. 27,31-35

#### *Pharmacologic Therapy - Bronchodilator Drugs*

The primary pharmaceutical agents used to control the symptoms of COPD are bronchodilators.  $\beta_2$  adrenergic agonist, methylxanthines, and anticholinergics are the class of bronchodilators available for the treatment of acute COPD exacerbations. These therapeutic agents reduce bronchospasms and airway contraction, thoracic and lung hyperinflation, and air

trapping within the lung. Since these drugs prevent hyperinflation of the lungs, the FEVI is significantly improved. 2, 27, 33

Short acting  $\beta_2$  adrenergic agonists are first choice of treatment for COPD patients with intermittent symptoms and acute exacerbations. These drugs have a rapid onset of actions, induce bronchodilation and relaxation of the airway smooth muscles, improve lung function, and exert their action for 4 to 6 hours.  $\beta_2$  adrenergic agonists prevent smooth muscle contraction and bronchospasm by binding to  $\beta_2$  adrenergic receptors in the airway smooth muscles and stimulating adenylyl cyclase to increase intracellular concentrations of cyclic adenosine monophosphate (cAMP), a downstream signaling molecule. cAMP mediates bronchodilation by decreasing intracellular concentration of calcium, be it by sequestering them into calcium stores or removing them from the cell. When intracellular concentrations of calcium are decreased, they are unable to bind to calmodulin, phosphorylate myosin light chain kinase, and induce smooth muscle contraction. Short-acting  $\beta_2$  adrenergic agonists such as albuterol, levalbuterol, and pirbuterol are the most preferred and widely used bronchodilators for acute COPD exacerbations, and bronchoconstriction. Inhalation is the preferred route of administration, and these drugs can be delivered via nebulizer, metered dose inhaler, or a dry powder inhaler. Oral or parenteral routes increase the risk of systemic adverse effects such as increased heart beat, palpitations, nausea, and hand tremors, and thus should not be used to treat COPD exacerbations. 2, 27, 33, 36-40

Long acting  $\beta_2$  adrenergic agonists such as salmeterol, arformoterol, and formoterol are recommended for patients with advanced cases of COPD, or patients unresponsive to short acting  $\beta_2$  adrenergic agonists. Long acting  $\beta_2$  adrenergic agonists reduce the symptoms and frequency of COPD exacerbations. These therapeutic agents effectively induce bronchodilation for 12 hours, and thus are prescribed to alleviate breathing difficulties while sleeping. In addition to bronchodilation, long acting  $\beta_2$  adrenergic agonists significantly improve lung function, specifically FEVI, and reduce the frequency of COPD exacerbations. Formoterol and arformoterol have a rapid onset of action, while salmeterol has a slower onset, typically between 15 to 30 minutes. Formoterol is also a full agonist, meaning a smaller amount of the ligand is required to bind to the receptor to produce maximum effects, whereas salmeterol is a partial agonist, meaning a greater fraction of the agonist is required to bind to the receptor to achieve

maximum effects. Prolonged or chronic use of long acting inhaled  $\beta_2$  adrenergic agonists has been shown to cause a desensitization of  $\beta_2$  adrenergic receptors and decrease the binding affinity of the ligand to its receptors. The down-regulation of  $\beta_2$  adrenergic receptor decreases the duration of bronchodilation and smooth muscle relaxation. As a result, long acting  $\beta_2$  adrenergic agonists are typically prescribed in conjunction with a short acting  $\beta_2$  adrenergic agonists for acute exacerbations and not used for prolonged durations of time. 2, 27, 33, 37

Ipratropium is the primary short acting anticholinergic bronchodilator used for the treatment of COPD in the United States. It is the leading prescribed anticholinergic bronchodilator, and is often used in conjunction with a  $\beta_2$  adrenergic agonists to produce bronchodilation in the airways. Anticholinergic agents such as ipratropium bromide inhibit bronchoconstriction by acting as an antagonist to acetylcholine and binding to muscarinic cholinergic receptors. Acetylcholine is a chemical messenger released by the vagus nerve upon exposure to noxious particles, or irritants such as cigarette smoke. This chemical upregulates the expression of muscarinic 1 and 3 receptors, and once it binds to these receptors, it mediates the cholinergic effect, including airway narrowing, bronchoconstriction of airway smooth muscles, mucus hypersecretion, activation and infiltration of neutrophils to the airways, and thickening and proliferation of airway smooth muscle. Ipratropium bromide competitively binds to muscarinic 1 and 3 receptors, and inhibits contraction of the airway smooth muscles, and airway narrowing. It has a slower onset of action than a standard short-acting  $\beta_2$  adrenergic agonist such as albuterol, but it has a duration of 4 to 6 hours. There is no systemic absorption of ipratropium bromide, thus systemic side effects such as nausea, tachycardia, and blurry vision are not observed. 2, 27, 33, 41- 43

Tiotropium bromide is a long acting anticholinergic bronchodilator prescribed for patients with persistent and chronic COPD exacerbations. Similar to ipratropium bromide, this bronchodilator binds to muscarinic receptors in the smooth muscles of the airways, as well as the mucus glands, and prevents mucus hypersecretion and bronchoconstriction. Tiotropium bromide is more selective than ipratropium bromide, and acts by prolonged blockade of M3 and M1 receptors, thereby prolonging its primary therapeutic effect, bronchodilation. Furthermore, studies have revealed that the binding of tiotropium bromide to M3 and M1 receptors is 10 times as potent as the binding of ipratropium bromide to these receptors in the lungs. As a result,

tiotropium bromide protects against bronchoconstriction for minimum of 24 hours, and is administered once daily. 2, 27, 33, 41, 42

Theophylline and aminophylline are methylxanthines used for the treatment of COPD. These drugs induce bronchodilation by inhibiting the action of phosphodiesterase-4 (PDE4) and Phosphodiesterase-3 (PDE3), and increasing the intracellular concentration of cAMP and cGMP and consequently, decreasing intracellular concentrations of calcium. These drugs also suppress the recruitment of inflammatory cells such as CD8+ T cells, macrophages, and neutrophils to the airways, and inhibiting the release of protease and mediators from mast cells, neutrophils and leukocytes. Theophylline and aminophylline act as an agonist to adenosine receptors, and prevent the release of bronchoconstrictive agents such as histamine, and leukotrienes via the degranulation of mast cells. Methylxanthines such aminophylline and theophylline are extremely useful for patients who are unresponsive to inhaled  $\beta_2$ -agonists and inhaled anticholinergics. They improve lung function, gas diffusion, the FEV1 and vital capacity of the lungs. Chronic use of these drugs are controversial and not recommended since there is a higher incidence of side effects such as nausea, vomiting, and headaches. 2, 27, 33, 44-52

### *Antimicrobial Therapies*

Pathogenic infections in the lower respiratory tract are implicated in acute exacerbations of chronic bronchitis and emphysema. Impairment of mucociliary clearance enables pathogenic organisms such M. catarrhalis, H. influenza, and S. pneumonia to colonize and thrive in the lower respiratory tract. These bacterial organisms increase mucus secretion, further impair normal ciliary activity, and complicate the underlying disease. Antibiotics such as doxycycline, amoxicillin-clavulanate potassium, and trimethoprim-sulfamethoxazole are administered to COPD patients with acute bacterial infections, and is used to treat COPD exacerbation accompanied with fever, cough and increased sputum. 27,53-54

### *Alpha1-antitrypsin Replacement Therapy*

Alpha1-antitrypsin deficiency is an inherited disorder that significantly increases an individual's risk for developing emphysema. For patients with alpha1-antitrypsin deficiency associated emphysema, the initial treatment focuses on reducing the risk factors for developing

emphysema, primarily smoking, and treating the symptoms of emphysema with bronchodilators, and alpha1-antitrypsin replacement therapy. Since alpha1-antitrypsin deficiency is characterized by extremely low serum levels of this anti-protease, alpha1-antitrypsin augmentation therapy ensures that the serum concentration of alpha1-antitrypsin is above the protective threshold. 27

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