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Bronchitis

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Introduction

Bronchitis is characterized by bronchial inflammation that results in **cough** and sputum production. This inflammation can be acute in nature, usually resulting from a viral infection, or it may be a long-standing manifestation of **chronic obstructive pulmonary disease**. Acute infectious bronchitis differs from chronic bronchitis with respect to etiology, pathophysiology, and treatment.

Definition

Acute bronchitis is among the most frequent reasons for visits to the physician's office. It can be defined as an infectious, generally viral, respiratory illness that last for 1-3 weeks that occurs in an otherwise healthy adult with cough as the predominate feature [Gonzales and Sande \(2000\)](#). In addition to cough and usually sputum production, acute bronchitis frequently involves upper respiratory symptoms and constitutional complaints, such as fatigue and body aches. An illness comprised of these symptoms may be classified as acute bronchitis once the diagnosis of **pneumonia** is excluded.

As a form of chronic obstructive pulmonary disease (COPD), chronic bronchitis is characterized by irreversible or incompletely reversible airway obstruction that produces a decrease in maximal expiratory airflow [Chitkara and Sarinas \(2002\)](#). The definition of chronic bronchitis is symptomatic. That is, it is a condition that results in a mucus-producing cough that is present for at least 3 months of the year for 2 consecutive years and does not have some other underlying etiology such as **tuberculosis** [Wisniewski \(2003\)](#). Depending on its severity, chronic bronchitis may produce minimal to significant functional impairment.

Classification

Acute bronchitis is a form of lower respiratory tract infection [Gonzales and Sande \(2000\)](#). Although an etiology is formally identified in only a small percentage of clinical cases, the identity of the disease-producing organism may be used to classify acute bronchitis.

Chronic bronchitis is the most common form of chronic obstructive pulmonary disease (COPD), a group of conditions involving airway obstruction, decreased maximal expiratory airflow, and breathing-related symptoms. Emphysema, or destruction of the alveoli, is the other major manifestation of COPD [Chitkara and Sarinas \(2002\)](#). Nonremittant **asthma**, involving bronchoconstriction that is irreversible or only partially reversible, may also be classified as COP D. It is not unusual for individuals to experience combined forms of COPD involving sputum production, alveolar destruction, and bronchospasm.

COPD can be classified on the basis of severity [Pauwels et al \(2001\)](#). Stage 0 (at risk) is characterized by normal spirometric readings and the presence of chronic cough and/or sputum production. Stages I, II, or III COPD is present if the forced expiratory volume in 1 second divided by the forced vital capacity (FEV_1/FVC) is less than 70%. Chronic

cough and/or sputum production may or may not be present. In stage I (mild COPD), the FEV₁ is at least 80% of the predicted value. In stage II (moderate COPD), the FEV₁ is above 30%, but less than 80% of the predicted value. Stage III (severe COPD) is defined by an FEV₁ below 30% of the predicted value or the presence of respiratory failure or right-sided heart failure.

Acute exacerbations of chronic bronchitis are associated with worsened dyspnea, elevated sputum production, and increased sputum purulence. These can be classified as severe (type 1) if all three of symptoms are present and moderate (type 2) if two of the three are present. A mild exacerbation is diagnosed if one of the above symptoms occurs along with at least one of the following: upper respiratory tract infection in the past 5 days, fever without other apparent cause, increased wheezing, increased cough, and respiratory rate or heart rate elevated at least 20% above baseline.

Consequences

Both acute and chronic bronchitis give rise to a persistent, sputum-producing cough. Bronchial hyperresponsiveness, wheezing, and difficulty breathing (dyspnea) may occur, and difficulty breathing upon exercise (exertional dyspnea) is fairly common.

In most cases of acute bronchitis, the symptoms of cough and sputum production last for 1 to 3 weeks [Gonzales and Sande \(2000\)](#). Infections such as otitis media, **sinusitis**, and, more rarely, pneumonia may result from either the primary viral infection or a secondary bacterial infection. Acute bronchitis resulting from influenza may additionally produce more rare complications of muscular inflammation (myositis) and muscle cell lysis leading to potentially fatal renal damage (rhabdomyolysis). Additional consequences of acute bronchitis are seen in children. **Reye syndrome** may occur in children with influenza, particularly if they are treated with **aspirin**. Viral lower respiratory infection in early life has been associated with the later development of asthma [Gern \(2000\)](#).

In contrast to acute bronchitis, which resolves following the termination of the causative infection, chronic bronchitis generally worsens with time, even with optimal treatment [Chitkara and Sarinas \(2002\)](#). Cessation of exposure to a triggering stimulus, such as tobacco smoke, is the only currently available therapeutic management that can slow the progression of chronic bronchitis. Usually, by the time treatment is sought, there is irreversible damage to **the lungs**.

Progression of chronic bronchitis leads to shortness of breath, initially manifesting only during exercise but also occurring at rest as the disease worsens. Increasing pulmonary dysfunction can result in pulmonary hypertension, right ventricular enlargement, and right-sided heart failure (cor pulmonale). Signs of cor pulmonale include peripheral edema, enlargement of **the liver** and other internal organs, and increased breathing difficulty. Weight loss may occur, and muscle wasting can contribute to the development of exercise intolerance.

An individual affected with chronic bronchitis is susceptible to repeated episodes in which the symptoms of cough, sputum production, and dyspnea worsen [McCroary et al \(2001\)](#). These episodes, termed acute exacerbations of chronic bronchitis, may result from viral or, more rarely, bacterial infection. Environmental exposure to tobacco smoke, air pollutants, or allergens may also produce acute exacerbations of chronic bronchitis. The cause of approximately one-third of acute exacerbations is unknown.

Associated Disorders

Acute bronchitis is a very common respiratory illness. An elevated risk for the development of acute bronchitis is seen among the very young and the elderly, smokers,

immunocompromised individuals, persons with comorbid conditions, such as **diabetes**, cardiovascular disease, pulmonary disease, and alcoholics [Gonzales and Sande \(2000\)](#). These individuals are also at higher risk of developing complications of acute bronchitis, such as pneumonia.

Chronic bronchitis is the most common form of chronic obstructive lung disease (COPD), with emphysema (alveolar destruction) being the next most frequently observed manifestation. Nonremittant asthma may also be classified as COPD. It is common for individuals with COPD to exhibit characteristics of chronic bronchitis, emphysema, and/or bronchospastic disease.

Individuals with COPD are more susceptible to lower respiratory infections such as acute bronchitis and pneumonia [Ward and Casaburi \(2001\)](#), [Chitkara and Sarinas \(2002\)](#). In more advanced disease, they may develop **pulmonary hypertension**, resulting in right ventricular enlargement and, as the disease progresses, right-sided heart failure (cor pulmonale).

Etiology

Acute bronchitis is usually caused by viruses associated with lower respiratory tract infections, including **influenza A** and B, parainfluenza, **respiratory syncytial virus**, and human metapneumovirus and upper respiratory tract infections, such as rhinovirus, corona virus, and adenovirus [Bandi et al \(2001\)](#). The most common cause of acute bronchitis is influenza, with a much smaller percentage of acute bronchitis cases resulting from bacterial infection. *Chlamydia pneumoniae* has been responsible for several recent outbreaks, particularly in young adults. *Bordetella pertussis* may cause atypical symptoms resulting in prolonged cases of acute bronchitis in previously immunized adults. *Mycoplasma pneumoniae* is an additional established etiologic agent of acute bronchitis. There is very little evidence that acute bronchitis may be caused by bacterial species that are characteristic of pneumonia infections (e.g., *Streptococcus pneumoniae*). Chronic bronchitis most frequently develops in tobacco smokers, approximately 30-50% of whom eventually show symptoms of this disorder [Viegi \(2001\)](#). Passive exposure to smoke can also contribute to the development of chronic bronchitis. Other causative factors include exposure to indoor or outdoor air pollution, occupational dusts (e.g., grain, coal), or chemical irritants (e.g., sulfur dioxide). Chronic bronchitis may also develop in people with a history of recurrent lung infections or airway hyperresponsiveness [Hogg \(1999\)](#). Acute exacerbations of chronic bronchitis are commonly associated with influenza, parainfluenza, coronavirus, or rhinovirus infections [McCrory et al \(2001\)](#). Elevated levels of particulate air pollution and ozone are also associated with acute exacerbations. The role of bacterial infection in acute exacerbation of chronic bronchitis remains controversial. Pathogenic bacterial such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* are present in the sputum of approximately half of all those experiencing acute exacerbations but are also frequently present during periods of stable disease [Hirschmann \(2000\)](#). **Clinical trials** have shown that antibiotic therapy is helpful in 40% or less of those with acute exacerbations. However, in the subset of exacerbations in which purulent sputum is a predominant feature, the extent of bacterial eradication correlates with the degree of resolution of the exacerbation and its associated inflammation [White et al \(2003\)](#). Thus, an increase in bacterial load, acquisition of a new bacterial pathogen, or a change in the antigenic makeup of the resident bacterial population, may be responsible for certain acute exacerbations of chronic bronchitis. The role of bacterial infection in the progression of chronic bronchitis is unclear [Wilson \(1998\)](#).

Epidemiology

Acute bronchitis is a widespread condition that usually occurs in outbreaks and epidemics, especially during the winter months. Its incidence is approximately 50–60 cases per 1,000 persons per year [File \(2000\)](#). An elevated risk for the development of acute bronchitis is seen among the very young and the elderly, smokers, immunocompromised individuals, persons with comorbid conditions, such as cardiovascular or pulmonary disease, and alcoholics. Such individuals are also at increased risk for developing complications such as pneumonia.

Chronic bronchitis and emphysema are related manifestations of chronic obstructive pulmonary disease (COPD) and often coexist in an individual. According to the 2001 National Health Interview Survey, 9.2 million Americans have been diagnosed with chronic bronchitis, 2 million with emphysema, and 0.9 million with both [Barnes et al \(2003\)](#). In the US, COPD is the primary cause of death for over 120,000 people a year. A large number of cases may be undiagnosed, as a recent survey involving the direct measurement of pulmonary function suggests that nearly 24 million individuals in the US suffer from COPD [Mannino et al \(2002\)](#).

Chronic bronchitis is most commonly seen in individuals over the age of 40. It is more common in women than men across all age groups and may be more severe in women [Barnes et al \(2003\)](#). In the 25–44 and 65+ age groups, it is more common in whites than blacks, whereas the reverse is true in the 45–64 age group.

The most significant risk factor for the development of chronic bronchitis is cigarette smoking, with morbidity and mortality increasing in proportion to the extent and duration of smoking [Viegi \(2001\)](#). Occupational exposures to dusts (e.g., coal, grain, and cadmium and other heavy metals) and industrial chemicals (e.g., isocyanates, certain adhesives, and welding fumes) also pose significant risk for the development of chronic bronchitis. Environmental tobacco smoke and air pollution are also associated with an increased risk of developing COPD.

A history of childhood respiratory infections correlates with an increased risk of COPD [Hogg \(1999\)](#). Latent infection with adenovirus may enhance the inflammatory response to environmental causes of chronic bronchitis, as may infection with the ulcerogenic bacterium *Helicobacter pylori* [Roussos et al \(2003\)](#). Colonization of the lower airways with *Haemophilus influenzae*, a pulmonary pathogen, may be associated with chronic bronchitis and its acute exacerbations [Wilson \(1998\)](#), [Bandi et al \(2001\)](#).

Host factors are also involved in the development of COPD. Low socio-economic status, high alcohol consumption, and a tendency toward atopic allergic reactions and hypersensitivity are associated with COPD [Viegi \(2001\)](#). Low dietary intake of fresh fruit and vegetables, antioxidants such as vitamin C and beta-carotene, fish, and omega-3 fatty acids has also been associated with impaired lung function [Romieu and Trenga \(2001\)](#). An inherited deficiency in alpha-1 antitrypsin (alpha-1 proteinase inhibitor) results in early-onset emphysema [Viegi \(2001\)](#). Genetic factors may also be involved in the development of chronic bronchitis in general.

Pathophysiology

The signs and symptoms of acute bronchitis result from the pathogen itself and from the immune response to the infection.

The acute phase of this illness lasts from 1–5 days and involves constitutional symptoms such as **fever**, fatigue, and muscle aches [Gonzales and Sande \(2000\)](#), [Balter \(2001\)](#). It is during this phase that viral colonization of the tracheobronchial epithelium occurs. In

response to this infection airway epithelial cells and resident monocytes and macrophages release cytokines that recruit and activate immune cells. Infection with influenza A virus provides an example of this process. Influenza A infection stimulates the release of chemotactic chemokines including **RANTES**, monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1alpha (MIP-1alpha), pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin-1beta, (IL-1beta), IL-6, and IL-18, and antiviral cytokines such as **interferon-alpha (IFN-alpha)** and **IFN-beta** [Julkunen et al \(2001\)](#). Neutrophils are among the first cells recruited to the tracheo-bronchial epithelium, and their increased number correlates with the development of airway hyperresponsiveness. T lymphocytes are recruited and activated by RANTES and other cytokines released by monocytes. Eosinophils are recruited and activated and may persist for weeks after the initial infection.

The protracted phase of acute bronchitis involves coughing, wheezing, and sputum production and lasts from 1-3 weeks. It frequently involves a significant decline in pulmonary function that can be measured as a decrease in the forced expiratory volume in 1 second (FEV₁). The bronchial hyperresponsiveness, which was initiated during the acute phase, persists for several weeks and correlates with the extended presence and activation of inflammatory cells.

The pathological hallmark of chronic bronchitis is airflow limitation secondary to inflammation and increased mucus production in the large (>2 mm) airways. The disease process begins when damage to the airways initiates inflammation and remodeling of the airway epithelium, leading to mucus hypersecretion, obstruction of the airways, and increased susceptibility to bacterial colonization [MacNee \(2000\)](#), [Turato et al \(2001\)](#), [Cosio-Piqueras and Cosio \(2001\)](#). The presence of pathogenic bacteria in the lung is a common cause of acute exacerbations of chronic bronchitis and may also be related to disease progression. An ongoing cycle ensues in which inflammation and infection produce further epithelial damage, which perpetuates additional inflammation and airway remodeling.

Chronic bronchitis is initiated when repeated exposure to tobacco smoke, environmental lung irritants (e.g., coal or grain dust, air pollutants), and/or respiratory infections produce damage in the large airways. Recruitment of inflammatory cells results from up-regulation of adhesion molecules such as ICAM-1 and E-selectin on the subepithelial blood vessels. Neutrophils are the predominant cell type recruited into the lumen of the airways. Macrophages and CD8+ T lymphocytes are the predominant cells that infiltrate the subepithelial space. Eosinophils are prevalent in the subepithelium during acute exacerbations of chronic bronchitis, while large numbers of neutrophils are seen here only in severe disease. While enlargement of the mucous glands was formerly believed to be a defining feature of chronic bronchitis, it is now believed that inflammation of these glands is more characteristic.

Inflammatory cells in the airway lumen and epithelium release mediators that control the inflammation and airway remodeling that is characteristic of chronic bronchitis [Reid and Sallenave \(2003\)](#). Neutrophils release reactive oxygen species such as superoxide and peroxynitrite that produce tissue damage and further inflammation. Elevated levels of pro-inflammatory molecules, such as IL-8, LTB₄, and TNF-alpha, and diminished levels of the anti-inflammatory cytokine IL-10 are seen in the sputum of individuals with chronic bronchitis. Elevated levels of the mucus-stimulating cytokines IL-4 and IL-13 are seen in patients with chronic bronchitis. Neutrophils in the airways release neutrophil elastase, a serine protease that increases the production of mucus and stimulates the proliferation of mucus-producing goblet cells. Squamous metaplasia occurs, resulting in the replacement of many ciliated columnar epithelial cells with squamous epithelial cells. Overall, these processes of excessive bronchial mucus secretion and impaired clearance result in airway obstruction, irritation, and an increased likelihood of infection.

Many similarities exist between the processes occurring in the large and small (<2 mm) airways of those with chronic bronchitis. Subepithelial infiltration of CD8+ T lymphocytes and goblet cell proliferation contribute to inflammation and mucus secretion, respectively. In addition, fibrosis of the airway walls decreases the elastic recoil of the lung, while hypertrophy of the bronchiolar smooth muscle produces airflow restriction. Attachments of the alveoli to the bronchioles may be lost as well.

In the pulmonary arteries, chronic bronchitis causes proliferation of smooth muscle cells and deposition of elastic and collagen fibers [Turato et al \(2001\)](#). This appears to be the result of endothelial dysfunction that results from hypoxemia or other, unknown factors. Pulmonary hypertension occurs as a consequence of pulmonary artery narrowing, and the right ventricle may become enlarged as a result of prolonged pumping against elevated arterial pressure. Right ventricular failure (cor pulmonale) is a common complication of chronic bronchitis.

Signs and Symptoms

The initial, acute phase of acute bronchitis begins with 1-5 days of constitutional symptoms such as fever, malaise, and muscle aches [Gonzales and Sande \(2000\)](#). These symptoms are variable in extent and duration, and depend upon the nature of the infectious agent. For example, rhinovirus infection produces minimal or no constitutional symptoms whereas influenza and parainfluenza produce the most severe and prolonged symptoms. The protracted phase of acute bronchitis lasts for 1-3 weeks and involves coughing, increased sputum production, and wheezing.

Acute bronchitis is distinguished from upper respiratory infections by the presence of cough, sputum, and wheezing with the former. The signs and symptoms of acute bronchitis differ from those of pneumonia in that pneumonia causes abnormal lung sounds that indicate the presence of fluid (e.g., rales) and elevations in vital signs (heart rate >100 beats/minute, respiratory rate >24 breaths/minute, and temperature >38° C). While pneumonia can be confirmed with radiography, this is unwarranted in low-risk individuals who have elevated vital signs without abnormal lung sounds, particularly during a known viral outbreak. X-ray testing in the absence of abnormal lung sounds may be necessary in the elderly and in those with co-morbidities that place them at high risk of pneumonia and other complications.

Chronic bronchitis is a manifestation of chronic obstructive pulmonary disease (COPD) involving cough and sputum production, with or without wheezing, that lasts for at least 3 months for 2 consecutive years [Chitkara and Sarinas \(2002\)](#). It most frequently appears in smokers over the age of 40 and is associated with acute exacerbations in which coughing, wheezing, and sputum production are increased. Persons with chronic bronchitis are at increased risk of developing pneumonia and other respiratory infections. Significant difficulty breathing during exercise, and, as the disease progresses, also at rest usually manifest during the mid-sixties to early seventies.

Spirometric measurement of the forced expiratory volume in 1 second (FEV₁) and the forced vital capacity (FVC) may be used to assess pulmonary function and to stage the severity of COPD [Pauwels et al \(2001\)](#), [Lenfant and Khaltayev \(2003\)](#). A complete blood count can be used to rule out infection and may reveal an elevation in red blood cells resulting from chronic hypoxemia (polycythemia). A sputum culture may be used to check for acute infection. A chest X-ray can be performed to exclude other causes of cough such as pneumonia and **lung cancer**. In severe cases of chronic bronchitis, radiography may reveal right ventricular hypertrophy as well as enlargement and rapid tapering of the pulmonary arteries. If emphysema is present as well, each region of severe disease will be visible as a radiolucent area surrounded by a hairline shadow.

Acute exacerbations of chronic bronchitis are associated with worsened dyspnea and increased sputum production and purulence. Acute exacerbations can be classified as severe (type 1) if all three symptoms are present and moderate (type 2) if two of the three are present [McCrorry et al \(2001\)](#). A mild exacerbation is diagnosed if one of the above symptoms occurs along with at least one indicator of recent respiratory infection (e.g., fever, cough, and wheezing).

Standard Therapies

Because of its predominantly viral nature, acute bronchitis is best treated symptomatically, unless an influenza etiology is established and antiviral treatment is initiated early enough to ensure effectiveness. Antibiotics are useful in cases where bacterial infection is confirmed.

The medications available for the treatment of chronic bronchitis/chronic obstructive pulmonary disease (COPD) do not decrease the progressive decline in respiratory function that is characteristic of this condition. Rather, they only lessen its symptoms and their complications. The only intervention that slows the progression of COPD is decreased exposure(s) to substances that worsen this condition such as tobacco smoke, occupational dusts and chemicals, and air pollutants.

Agent Name	Discussion
Aids to smoking cessation	Smoking cessation is the most significant intervention that has the potential to slow the progression of chronic obstructive pulmonary disease Chitkara and Sarinas (2002) . Pharmacological therapy for tobacco dependence is added to counseling to increase the likelihood of success. Nicotine replacement therapy is most commonly given as a transdermal patch, with nicotine gum, nasal spray, inhaler, or lozenge used to counteract breakthrough cravings. Smoking cessation is more likely to succeed when nicotine replacement therapy is used in combination with the antidepressant bupropion. With this combination, nicotine is gradually withdrawn while bupropion is maintained for 12 months or longer.
Beta-2 adrenoceptor agonists	Those with acute bronchitis frequently exhibit wheezing and other signs of reversible bronchoconstriction. Although chronic obstructive pulmonary disease is characterized by bronchoconstriction that is incompletely reversible following administration of a bronchodilator, long-term therapy with bronchodilators decreases the symptoms of airflow limitation in individuals with chronic bronchitis. Thus, bronchodilator therapy is central to the management of chronic bronchitis and its acute exacerbations Chitkara and Sarinas (2002) . Inhalation is the preferred route of administration because it maximizes the delivery of the agent to the lungs and minimizes systemic side effects. Short-acting beta-2 adrenoceptor agonists such as albuterol produce rapid bronchodilation by action on the beta-2 adrenoceptors on the airway smooth muscle. Anticholinergics are the preferred drugs for the treatment of acute bronchitis Smuncy et al (2003) . In the treatment of chronic bronchitis, beta-2 adrenoceptor agonists may be used on a scheduled basis or as-needed to treat acute bronchospasm. Beta-2 adrenoceptor agonists are also used in the treatment of acute exacerbations of chronic bronchitis McCrorry et al (2001) . The efficacy of long-acting beta-2 adrenoceptor agonists such as salmeterol is under study. The bronchodilatory effect of anticholinergics is additive with that of beta-2 adrenoceptor agonists. Combination products that deliver a metered dose of a beta-2 adrenoceptor agonist and ipratropium can simplify drug administration.

Anticholinergics	<p>Those with acute bronchitis frequently exhibit wheezing and other signs of reversible bronchoconstriction. Although chronic obstructive pulmonary disease is characterized by bronchoconstriction that is incompletely reversible following administration of a bronchodilator, long-term therapy with bronchodilators decreases the symptoms of airflow limitation in individuals with chronic bronchitis. Thus, bronchodilator therapy is central to the management of chronic bronchitis and its acute exacerbations Chitkara and Sarinas (2002). Inhalation is the preferred route of administration because it maximizes delivery of the agent to the lungs and minimizes systemic side effects. Anticholinergic bronchodilators such as ipratropium block the muscarinic receptor-mediated bronchoconstriction, mucus secretion, and bronchial vasodilation that result from vagal stimulation of the airways. The duration of action of ipratropium is longer than that of the short-acting beta-2 adrenoceptor agonist bronchodilators. It can decrease the volume of sputum produced without altering its viscosity. An ipratropium inhaler may be used in acute bronchitis where bronchospasm is problematic Smuncy et al (2003). In chronic bronchitis, ipratropium is a mainstay of therapy Chitkara and Sarinas (2002). Some individuals who are non-responsive to beta-2 adrenoceptor agonists derive symptomatic relief with ipratropium. The bronchodilatory effect of ipratropium is additive with that of beta-2 adrenoceptor agonists. Combination products that deliver a metered dose of a beta-2 adrenoceptor agonist and ipratropium can simplify drug administration.</p>
Theophylline	<p>Although chronic obstructive pulmonary disease is characterized by bronchoconstriction that is incompletely reversible following administration of a bronchodilator, long-term therapy with bronchodilators decreases the symptoms of airflow limitation in individuals with chronic bronchitis. Thus, bronchodilator therapy is central to the management of chronic bronchitis and its acute exacerbations Chitkara and Sarinas (2002). Theophylline exerts a wide variety of physiological actions including central nervous system stimulation, cardiac stimulation, and smooth muscle relaxation. Its major action on the lung results from the inhibition of the cyclic nucleotide phosphodiesterases that break down cyclic AMP and cGMP, second messengers that mediate bronchodilation. Theophylline also inhibits the release of inflammatory mediators by immune cells. Its narrow therapeutic index, potentially life-threatening side effects, and numerous drug interactions have made theophylline a second-line therapy for chronic bronchitis. While its efficacy as compared to other bronchodilators is questionable, a subset of patients appears to benefit from theophylline. Lower therapeutic doses used in combination with a beta-2 adrenoceptor agonist may be beneficial in some cases.</p>
Oxygen	<p>Oxygen therapy is indicated when the symptoms of chronic obstructive pulmonary disease (COPD) become severe enough to limit activities of daily living Chitkara and Sarinas (2002). It may also be used as-needed during exercise in those who don't qualify for continuous oxygen use. Oxygen therapy reduces mortality and improves quality of life in persons with severe COP D. It is also useful in the management of acute exacerbations of chronic bronchitis McCroory et al (2001).</p>
Antibiotics	<p>Although antibiotics are frequently prescribed for acute bronchitis, most cases are viral in origin, rendering them useless. Antibiotic therapy does not decrease the duration of illness, limitation of activities, or loss of work time in most cases of acute bronchitis Fahey et al (1998), Smuncy et al (1998), Bent et al (1999). Thus, the frequency of antibiotic use can safely be reduced without affecting patient outcomes Gonzales et al (2001). In the rare cases in which acute bronchitis is caused by <i>Mycoplasma pneumoniae</i> or <i>Chlamydia pneumoniae</i>, fluoroquinolones, tetracycline, and macrolides are effective Gonzales and Sande (2000). Acute bronchitis caused by <i>Bordetella pertussis</i> may be treated with erythromycin, but it is only effective early in the course of illness. The role of bacterial infection in acute exacerbation of chronic bronchitis remains</p>

	<p>controversial. In those exacerbations in which purulent sputum is a predominant feature, the extent of bacterial eradication correlates with the degree of resolution of inflammation associated with the exacerbation White et al (2003). The United States National Heart, Lung, and Blood Institute and the World Health Organization recommended that antibiotics be given for acute exacerbations in which there is evidence of infection, e.g. increased sputum production, change in sputum color, and/or fever Pauwels et al (2001). Commonly used antibiotics include amoxicillin-clavulanate, azithromycin, and several cephalosporins and fluoroquinolones.</p>
Glucocorticoids	<p>Although glucocorticoids are frequently employed in the therapy of chronic bronchitis, their use is controversial Chitkara and Sarinas (2002). Glucocorticoids block immune cell activation, cytokine release, and mucus secretion in vitro, yet only 10-20% of individuals with chronic obstructive pulmonary disease actually respond to them. It is impossible to predict who will respond to glucocorticoids. Indeed, those who benefit from oral glucocorticoids during acute exacerbations may not realize any value from chronic inhaled glucocorticoid use. Systemic glucocorticoids (e.g., prednisolone) are used for the treatment of acute exacerbations of chronic bronchitis and can alleviate symptoms, decrease hospitalization time, and reduce relapse rate among steroid-responsive individuals McCorry et al (2001). Chronic treatment with inhaled glucocorticoids such as fluticasone produces a modest reduction in the incidence of acute exacerbations, with no impact on the rate of functional decline. The United States National Heart, Lung, and Blood Institute and the World Health Organization recommend long-term maintenance therapy with inhaled glucocorticoids in symptomatic patients who exhibit a documented spirometric response to glucocorticoids or who have an FEV-1 of <50% of predicted and suffer from repeated exacerbations requiring antibiotic or glucocorticoid therapy Pauwels et al (2001). Systemic glucocorticoids should be used in the management of acute exacerbation, but chronic treatment should be avoided due to the potential for severe adverse effects.</p>
Vaccines	<p>Because influenza vaccines significantly decrease morbidity and mortality in persons with chronic bronchitis, annual influenza vaccination is recommended Pauwels et al (2001). The pneumococcal vaccine has been used in patients with chronic bronchitis, but there are insufficient data to support its general use for this purpose.</p>
Non-steroidal antiinflammatory drugs	<p>Non-steroidal antiinflammatory agents such as ibuprofen and antipyretic pain relievers, such as acetaminophen, may be used to lessen the symptoms of the acute phase of acute bronchitis (e.g., fever, muscle aches) Gonzales and Sande (2000).</p>
Antiviral drugs	<p>In cases of acute bronchitis caused by influenza A, amantadine or rimantadine may be effective if given within 48 hours of the onset of symptoms Gonzales and Sande (2000). These drugs block the proton channel required for the dissolution of the viral ribonucleoprotein complex early in the process of replication. Zanamivir and oseltamivir are effective against influenza A and B and, like amantadine and rimantadine, must be taken within the first 48 hours of illness. These drugs inhibit neuraminidase, a viral surface glycoprotein involved in the release of progeny virus and in the spread of infection from cell to cell.</p>

Experimental Therapies

A large number of experimental therapies are under development for the treatment of chronic obstructive pulmonary disease. With the exception of novel antiinfective agents and the anticholinergic bronchodilator tiotropium, there are few experimental therapies under development for the treatment of acute infectious bronchitis.

Agent Name	Discussion
Mucolytic agents	Because mucus hypersecretion and impaired mucociliary clearance are characteristic of chronic bronchitis, attempts are being made to speed the transport of mucus up the bronchiotracheal tree Wegner (2001) . Oral expectorants such as guaifenesin are of little benefit in chronic obstructive pulmonary disease. N-acetylcysteine is an orally administered glutathione precursor that reduces the sulfhydryl bonds of mucus proteins. It has been shown to thin the sputum without producing significant improvement in pulmonary function. Preliminary studies suggest that n-acetylcysteine may reduce the frequency of acute exacerbations, an action that may be related to its efficacy as an antioxidant.
Heliox	Heliox is a mixture of helium and oxygen that changes pulmonary airflow from turbulent to laminar. It has been shown to decrease the work of breathing in severe, stable, chronic obstructive pulmonary disease and may potentially be useful in the treatment of acute exacerbations of chronic bronchitis Chitkara and Sarinas (2002) , Rodrigo et al (2002) .
Phosphodiesterase inhibitors	Phosphodiesterase-4 (PDE-4) is a cyclic AMP-specific phosphodiesterase that predominates in pro-inflammatory and immune cells. Cilomilast is a new, orally active, selective inhibitor of PDE-4. Initial studies of cilomilast revealed significant functional improvement of chronic obstructive pulmonary disease (COPD) with minimal side effects Giembycz (2001) . There is a significant decrease in the number of CD8+ and CD68+ inflammatory cells characteristic of COPD without alteration of sputum values or FEV-1 Gamble et al (2003) .
Novel anticholinergic agents	Tiotropium is an inhaled anticholinergic that is available in Europe and is pending FDA approval in the United States Barnes (2003) . It exhibits very slow dissociation from M-1 muscarinic receptors and M-3 muscarinic receptors , allowing it to provide once-daily dosing and a greater degree of stability in lung function than ipratropium . Tiotropium may be useful in acute or chronic bronchitis.
Leukotriene receptor antagonists	Leukotriene B-4 (LTB-4) is a mediator of neutrophilic inflammation that is elevated in the sputum of persons with chronic bronchitis. Several antagonists of LTB-4 receptors are in clinical development and may be useful in the treatment of chronic bronchitis Kilfeather (2002) .
Cytokines and cytokine inhibitors	A number of agents that act through cytokine pathways that mediate the symptoms of chronic obstructive lung disease (COPD) are under investigation Barnes (2003) , Reid and Sallenave (2003) . Interleukin-10 (IL-10), an anti-inflammatory cytokine, decreases in those with COPD. Clinical trials of IL-10 in various inflammatory disorders are underway. IL-10 may hold promise in chronic bronchitis as well. Interleukin-8 (IL-8) is a neutrophil-attracting cytokine that is elevated in the sputum of persons with COPD. Inhibitors of IL-8 and antagonists of its receptor, CXCR2 , are being developed and may be useful in the treatment of chronic bronchitis. Tumor necrosis factor-alpha (TNF-alpha) is a pro-inflammatory cytokine that activates various immune cells and stimulates the production of inflammatory cytokines and other mediators. Its levels are elevated in the sputum of individuals with COPD. Monoclonal antibodies directed against TNF-alpha, such as infliximab and recombinant soluble TNF-alpha receptor (etanercept) are effective in rheumatoid arthritis and other inflammatory disorders and may be useful in the management of chronic bronchitis.
Inhibitors of oxidative stress	N-acetylcysteine is a cysteine donor, enhancing the production of the antioxidant glutathione and decreasing oxidative stress. It has been shown to reduce the frequency of acute exacerbations of chronic bronchitis Wegner (2001) . Additional antioxidants, such as stable glutathione compounds and superoxide dismutase analogs, are in clinical development. Inducible nitric oxide synthetase (iNOS) is responsible for the production of peroxy-nitrite, a potent oxidative species released

	during inflammation. Inhibitors of iNOS are under development and may be useful in the treatment of chronic bronchitis.
Protease inhibitors	Inhibitors of proteases (e.g., elastase) that are released by neutrophils during the inflammatory processes of chronic obstructive pulmonary disease are under development Barnes (2003) . These compounds may slow the progression of emphysema that accompanies certain cases of chronic bronchitis.
Inhibitors of inflammatory signal transduction	The p38 mitogen-activated protein (MAP) kinase is involved in the expression of inflammatory cytokines and proteases involved in chronic bronchitis. Inhibitors of MAP kinase have been developed and may be useful in treating chronic bronchitis Barnes (2003) . Inhibitors of phosphoinositide-3 kinase-gamma (PI-3Kgamma), an enzyme involved in neutrophil activation, may also be of value. Inhibitors of the NF-kappaB signaling pathway are in development and may be tested for the treatment of chronic bronchitis.

Animal Models

Models of acute infectious bronchitis involve animals infected with a causative viral agent. For example, mice, ferrets, and chickens infected with influenza viruses are commonly used in the search for new anti-influenza drugs [Sidwell and Smece \(2000\)](#).

A number of animal models are commonly employed in the study of chronic bronchitis [Nikula and Green \(2000\)](#). Hamsters, dogs, or rats exposed to sulfur dioxide (SO₂) for 3-6 weeks develop clinical and histological signs of chronic bronchitis. Mice, rats, guinea pigs, dogs, sheep, and monkeys have been used to study the role of cigarette smoke in the development of chronic bronchitis and emphysema. Rats, mice, hamsters, and guinea pigs exposed to organic dusts (e.g., cotton dust) and bacterial endotoxin have been used to model occupational exposures, which result in chronic bronchitis and other forms of lung inflammation. Exposure to other substances such as nickel and nitric acid has also been examined.

Other Information – Web Sites

Lazarus, S.J., Experts strive to better define the pathophysiology of COP D. This article examines new directions in the study of COPD pathology: <http://www.medscape.com/viewarticle/464534>

Croxton, T.L., Weinmann, G.G., Senior, R.M., Wise, R.A., Crapo, J. D. and Buist, A.S., Clinical research in chronic obstructive pulmonary disease: needs and opportunities: http://www.nhlbi.nih.gov/meetings/workshops/copd_clinical.htm

United States Department of Health and Human Services, CDC, NCH S. 2001 National Health Interview Survey. This web site contains data on the prevalence of COPD symptoms in the United States and their impact on activity and daily life. It also has epidemiological information on a number of other medical conditions: <http://www.cdc.gov/nchs/nhis.htm>

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