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67 Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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SHORT VIEW SUMMARY

Definition
- Chronic lung disease with irreversible airflow limitation with reduced forced expiratory volume in 1 second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio
- Acute exacerbation indicated by acute change from a patient's baseline with increased dyspnea, sputum volume, or sputum purulence; number of changes clinically defines severity

Epidemiology
- Prevalence expected to reach 10% of the overall population and 50% of smokers; fourth leading cause of death worldwide
- Increased risk for acute exacerbation in winter
- Risk factors: cigarette smoking, environmental particulate matter, genetic predisposition

Pathogenesis
- Intermittent progressive airway inflammation; remodeling and loss of lung function
- Ciliary dysfunction; excess mucus production; impaired phagocytosis leading to bacterial colonization

Microbiology
- Airways of patients with stable disease are frequently colonized with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis;* respiratory syncytial virus is most frequent colonizing virus.
- Microaspiration in stable disease introduces oral anaerobes (e.g., *Prevotella* and *Veillonella* spp.) into lower airway.
- During acute exacerbation, bacteria or viruses or both may be isolated, with more gram-negative rods found with worsening lung function. "Atypical" bacteria are not frequently isolated. Acquisition of new pathogen is associated with exacerbation.

Diagnosis
- Acute exacerbation is defined by increased sputum purulence, volume, and dyspnea.

Therapy
- Use of bronchodilators has increased for mild exacerbation without antibiotic therapy.
- Oral or intravenously administered corticosteroids and early empirical antibiotic therapy are advised for moderate to severe exacerbations.

Prevention
- Avoid exposure to particulate matter and cease smoking.
- Administer influenza, pneumococcal, and pertussis vaccines.
- Prescribe prophylactic daily azithromycin in patients with advanced disease with a history of exacerbation and no cardiac risk factors.

EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis, has been the third leading cause of death since 2008 in the United States.[1] It will become the third leading cause of death in the world by 2020.[2,3] COPD prevalence has increased owing to increased longevity and long-term exposure to common environmental risk factors such as inhaled particulate matter. By 2030, 10% of the general population and 50% of smokers will have COPD.[4,5,6] Consequently, COPD is an important driver of increased health care utilization, producing significant social and economic costs.[7-9]

COPD is caused by multiple factors, including environmental exposures, infections, inflammation, and genetic predisposition. Tobacco smoking is the largest environmental risk factor in the United States. In other countries, occupational dust exposures, outdoor air pollution, and poor indoor air quality from burning biomass fuels are major COPD risk factors.[10] Among immune-competent adults, increased airway bacteria produce airway inflammation and accelerate airway obstruction.[11] Immunosuppression is an independent risk factor for COPD. Immunoglobulin (Ig)A-deficient individuals have repeated lower respiratory tract infections during childhood and poor adult lung function.[12] Human immunodeficiency virus (HIV) infection promotes chronic pulmonary inflammation and increased pulmonary matrix metalloprotease expression, leading to smoking-related emphysema.[13,14] Even after effective antiretroviral therapy, patients with the acquired immunodeficiency syndrome (AIDS) have an increased frequency of pulmonary infection and accelerated lung function decline.[15,16] Genetic susceptibility is another risk factor for developing COPD. Mutation of the α_1-antitrypsin gene leads to low serum antiprotease activity, causing a much higher risk for COPD in smokers and workers exposed to particulate matter.[17] Homozygous α_1-antitrypsin deficiency (PI*ZZ) occurs in 1% to 4.5% of COPD patients, and the heterozygous form (PI*MZ), with less severe deficiency, occurs in 17.8% of COPD patients.[18] Ethnic origin is an important risk factor for COPD, raising the possibility of differential group-level genetic susceptibility to lung injury.[19] For most individuals, predisposition to abnormal lung function is polygenic, with more than 20 risk genes currently identified.[20,21] Poor socioeconomic status, chronic asthma, fetal growth retardation, poor nourishment, and history of pulmonary tuberculosis are other risk factors for COPD.[19,22-24]

Acute exacerbations of COPD (AECOPD) produce significant morbidity and mortality. Risk factors include viral and bacterial infections, change in environmental conditions such as smog, gastroesophageal reflux, lack of compliance with maintenance treatment, severity of baseline disease, and history of prior exacerbations.[25] Seasonality has been demonstrated in AECOPD, which occurs in northern and southern latitudes approximately two times more frequently during winter than in summer. AECOPD are responsible for the greatest proportion of health care–related costs associated with COPD.[7-9] The discussion in this chapter will focus on the impact of AECOPD on disease course, infectious causes of AECOPD, and treatment as well as prevention options.

CLINICAL MANIFESTATIONS

Patients with COPD usually present with progressive shortness of breath, cough, and sputum production. These symptoms are associated with accelerated decline in lung function, which may continue despite smoking cessation. The dyspnea usually starts during exercise but can occur with minimal exertion or at rest as disease progresses. Cough and sputum production are usually intermittent and more pronounced in the morning. Other chronic pulmonary diseases with similar clinical presentation and acute exacerbations should be differentiated from those of COPD because treatment differs. Examples of these include asthma, cystic fibrosis, bronchiectasis, diffuse panbronchiolitis, and obliterative bronchiolitis. Worsening symptoms, increased sputum volume, and transition of sputum color from clear to green or yellow suggests an acute exacerbation, which more commonly occurs during the winter.[26] The main differential diagnosis of exacerbations in patients with COPD includes pneumonia and congestive heart failure, both of which are common comorbidities in these patients.[4]

KEYWORDS

acute exacerbations of COPD (AECOPD); azithromycin; bronchitis; bronchodilators; chronic obstructive pulmonary disease (COPD); corticosteroid use in COPD; GOLD COPD summary; *Haemophilus*; lung inflammation; lung microbiome; microbiome; *Moraxella*; *Streptococcus pneumoniae*; therapy for COPD exacerbation; vaccinations

TABLE 67-1 Spirometric General Classification of COPD

SEVERITY	FEV_1/FVC	FEV_1 % PREDICTED
GOLD 0: At-risk patients who: Smoke or have exposure to pollutants Have cough, sputum, or dyspnea Have family history of respiratory disease	>0.7	≥80
GOLD 1: Mild COPD	≤0.7	≥80
GOLD 2: Moderate COPD	≤0.7	50-80
GOLD 3: Severe COPD	≤0.7	30-50
GOLD 4: Very severe COPD	≤0.7	<30

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

DIAGNOSIS

COPD is characterized by progressive airflow obstruction, defined by reduction of forced expiratory volume after 1 second (FEV_1) and a low ratio of FEV_1/forced vital capacity (FVC) on pulmonary function tests. Chronic bronchitis and emphysema are the two major clinical subtypes. Because overlap between them is common and treatment is similar, there is little clinical importance to distinguish chronic bronchitis from emphysema. Chronic bronchitis is defined by a history of productive cough for 3 months per year in at least 2 successive years. Emphysema used to be a pathologic diagnosis with distal airspace enlargement accompanied by destruction of alveolar walls. In the modern era, high-resolution computed tomography (CT) is able to define the extent and distribution of emphysema. With increasing use of CT to screen for lung cancer, more asymptomatic smokers are diagnosed with emphysema.[27]

Severity of stable COPD is based on pulmonary function (Table 67-1).[4] Initially, the results of standard pulmonary function tests are normal. Abnormalities in early disease may require more sensitive techniques that evaluate distal lung function, such as impulse oscillometry.[28] With progression, patients suffer decreasing FEV_1, decreasing FEV_1/FVC ratio, and increased total lung capacity caused by air trapping during expiration. Alveolar destruction promotes airway collapse and reduces diffusing capacity of carbon monoxide (D_LCO) in the lung. Eventually severe airflow obstruction can lead to abnormal arterial blood gases with hypoventilation (P_{CO_2} >40 mm Hg) and hypoxemia (P_{O_2} <60 mm/Hg). Integration of physiologic parameters with symptoms are useful, validated predictors of mortality.[29,30] One of the most commonly used composite criteria to accurately characterize COPD is called BODE. It includes *b*ody-mass index, airflow *o*bstruction (as defined by abnormal FEV_1), *d*yspnea, and *e*xercise capacity (evaluated by a 6-minute walk test).[31,32] BODE predicts response to rehabilitation, hospitalization, and mortality.[31,33-35]

Acute Exacerbations of COPD

Although there is no universal agreement on how to define or diagnose AECOPD, they are commonly defined as acute events with worsening respiratory symptoms beyond normal day-to-day variations. They usually require increased rescue β-agonist inhaler use to control symptoms.[36] One widely used scale to diagnose the presence and severity of AECOPD requires patients to have at least one of the following clinical presentations: upper respiratory tract infection symptoms within the previous 7 days, increased wheezing, fever without another identified cause, or an increase in heart rate or respiratory rate greater than 20% from baseline. This scale then categorizes patients into three groups based on whether they have worsening dyspnea, increase in sputum purulence, and/or increase in sputum volume. A severe exacerbation has all three criteria, a moderate exacerbation has two, and a mild exacerbation has only one.[37] Risk factors associated with COPD exacerbations include having three or more COPD exacerbations in the previous year, reduced FEV_1, smoking, and nonadherence with oxygen therapy.[38,39] The risk for severe exacerbation depends on each patient's medical history, including baseline FEV_1, number of prior exacerbations, prior need for mechanical ventilation, and comorbidities. Whereas the vast majority of AECOPD can be managed in the outpatient setting, the presence of high severity should prompt consideration of hospital admission.[4] The clinical signs of risk for respiratory failure are the most important measure of the current exacerbation's severity. Tachypnea (especially with a respiratory rate above 25 breaths/min), tachycardia, inability to speak full sentences, and fatigue are indications for hospitalization. Oxygen saturation above 90% can be misleading because hypoxemia is frequently a late event in the progression to respiratory failure. In an acutely symptomatic patient, arterial blood gas analysis is more useful than oximetry because it can diagnose hypercapnia as well as hypoxemia. Use of accessory muscles with paradoxical breathing characterized by inward motion of the abdomen during inspiration indicates diaphragmatic fatigue and impending respiratory failure. Abdominal paradoxical breathing, progressive hypercapnia, or deteriorating mental status usually indicates the need for ventilatory support in an intensive care unit with noninvasive or invasive positive-pressure ventilation.[4]

Additional diagnostic tests include chest radiography to identify pulmonary infiltrates and electrocardiography to assess for cardiac ischemia and arrhythmias, particularly paroxysmal atrial tachycardia. The basic metabolic panel is helpful to assess severity for AECOPD. Elevated levels of sodium bicarbonate are a sign of chronic hypercapnia. Increased anion gap is a sign of anaerobic metabolism of the respiratory muscles or sepsis syndrome or both. Hyponatremia sometimes occurs as a result of the syndrome of inappropriate secretion of antidiuretic hormone. Hyperglycemia is a response to stress or systemic corticosteroids, and renal insufficiency is a manifestation of reduced cardiac output in end-stage pulmonary hypertension. The presence of these derangements may warrant hospitalization.[4]

Radiology

Although chest radiography is an insensitive test to diagnose COPD, it is the usual first step in the evaluation of patients with progressive dyspnea and cough. It is useful to assess the symptomatic patient for advanced lung cancer, pulmonary fibrosis, or congestive heart failure. Sometimes COPD is suspected because the chest radiograph shows hyperinflation with flattened diaphragm or increased retrosternal space. If bullae are observed, then COPD is highly likely. CT is the imaging modality of choice for the evaluation of COPD and many other symptomatic pulmonary diseases. Data suggest that quantitative CT allows estimation of the risk for exacerbation frequency and determination of indices of disease impact such as BODE.[40]

PATHOPHYSIOLOGY

Impaired lung function in COPD is caused by destruction and remodeling of large and small airways due to chronic inflammation caused by complex interactions between the ambient (toxic inhalants, changing microbiome) and the airway mucosa (host immune response). Both inflammatory changes and lung function deterioration become more prominent with each exacerbation (Fig. 67-1). Early pathology is produced by inflammation in bronchioles less than 2 mm in diameter followed by parenchymal remodeling.[41,42] In early stages, the central airway walls are infiltrated with $CD8^+$ lymphocytes, producing bronchial wall thickening evidenced on chest CT.[43] Apoptosis and necrosis of epithelial and endothelial cells are also present, as are activated $CD4^+$ T cells.[44,45] As disease progresses, neutrophils become prominent and release neutrophil elastase, leading to parenchymal destruction.[46,47] Persistent airway injury also produces squamous metaplasia with loss of cilia function in affected bronchial segments. Disease of both the large and small airways contributes to airflow obstruction and ventilation heterogeneity.[48] Pulmonary hypertension due to loss of the pulmonary capillary bed can also develop in COPD. Chronic hypoxia also produces vasoconstriction, leading to fixed structural changes that worsen pulmonary hypertension.[49] As disease progresses, frequent exacerbations of COPD further contribute to increased lung inflammation and persistent loss of lung function.[50-54]

Mucosal Inflammation

COPD patients have a 20-fold increase in alveolar macrophages in alveoli, bronchioles, and small airways.[55,56] Because alveolar macrophages are a major source of inflammatory cytokines and growth factors, recruitment of inflammatory cells into the lung accelerates the

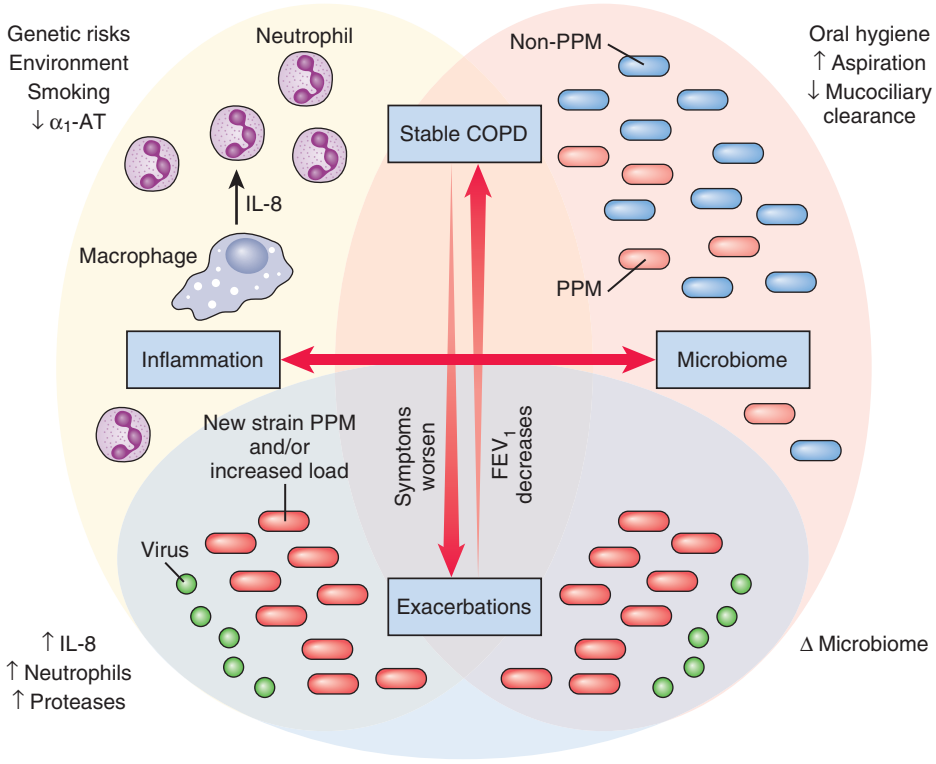


FIGURE 67-1 Chronic obstructive pulmonary disease (COPD) pathophysiology. α_1-AT, α_1-antitrypsin; FEV_1, forced expiratory volume in 1 second; IL-8, interleukin-8; PPM, potentially pathogenic microorganism.

vicious inflammatory cycle produced by microaspiration. In spite of increased numbers, alveolar macrophages have impaired phagocytosis, reducing their ability to clear bacteria from the lower airway and thereby causing further inflammation and oxidative stress.[57-60] Neutrophils are also recruited and activated by nonresolving pulmonary inflammation, particularly during exacerbations. Neutrophil elastase and metalloproteinases lead to lung parenchyma destruction. Neutrophil elastase is also a potent mucous secretagogue leading to mucous gland hyperplasia.[61] Because neutrophils have a short tissue life span, the airway neutrophilia observed in COPD requires continuous neutrophil recruitment.[62] Smoking also impairs neutrophil phagocytic function.[63] Collectins, pentraxins, and complement also are deficient,[64] further impairing mucosal immunity and predisposing to lower respiratory tract infections.

Pulmonary inflammation continues after smoking cessation, in part owing to permanent structural damage and in part owing to recovery of the proinflammatory capacity of epithelial cells.[65] Bacterial colonization in the lower airways is also an important determinant of the degree of airway and systemic inflammation in stable COPD.[66] Inflammatory mediators "spill over," producing systemic inflammation with elevated levels of C-reactive protein (CRP), fibrinogen, or leukocyte count. An elevated CRP level is most strongly associated with ischemic heart disease in smokers. Systemic comorbidities such as vascular disease are major risk factors for mortality during COPD exacerbations.[67,68] Systemic inflammation caused by COPD is also hypothesized to be associated with anemia, osteoporosis, depression, and the metabolic syndrome.[69-71]

Microbes in Stable COPD

Increased bacterial colonization of the lower airways in COPD occurs owing to chronic microaspiration, impaired clearance of bacteria, and frequent COPD exacerbations.[72,73] COPD patients frequently have microaspiration owing to gastroesophageal reflux due to incoordination between breathing and swallowing.[74-76] Impaired mucociliary clearance in smokers reduces the ability to clear oral microbes from the lower airways, exacerbating inflammation. This leads to chronic cough with progressive incoordination of breathing with swallowing. Inhaled medications may also carry oral bacteria into the lower airway. This vicious cycle could explain the association of poor oral health and increased airway bacterial load, COPD exacerbations, and reduced lung function.[77-81]

Viruses and bacteria in the lower airway perpetuate the inflammation in COPD, causing damage by a number of mechanisms.[11,82,83] They may be ciliotoxic, invade epithelial cells causing apoptosis, increase mucin production, or degrade humoral immunity via secretion of IgA proteases.[84,85] Bacterial molecules such as endotoxins, membrane lipoproteins, peptidoglycan fragments, and lipoteichoic acid activate the innate immune response, exacerbating inflammation.[86] COPD patients whose airways are heavily colonized with bacteria have higher concentrations of inflammatory cytokines and neutrophils in respiratory secretions.[83] High bacterial burden in the lower airway is associated with accelerated FEV_1 decline, more comorbidity, more exacerbations, and worse symptoms during exacerbations.[15,87,88-90]

In stable COPD, the rates of positive routine bacterial cultures of sputum vary between 22% and 83%.[91-93] However, interpreting sputum culture is difficult owing to upper airway contamination, which reduces specificity, and failure to grow fastidious bacteria from the complex lower airway microbiome, which reduces sensitivity. In stable COPD, nonpotential pathogenic microorganisms are isolated much more frequently than potential pathogenic microorganisms.[91] Nonpotential pathogenic microorganisms are usually oropharyngeal microbes such as *Corynebacterium* spp., *Neisseria* spp., *Enterococcus* spp., coagulase-negative staphylococci, *Streptococcus viridans,* and fungi such as *Candida* spp.[91] The most commonly isolated potential pathogenic microorganisms are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*[52,91,94] Culture-independent technologies that assay microbial nucleic acids and antigens often have found potential pathogens in culture-negative respiratory specimens.[95,96] For example, one third of stable COPD patients have *Haemophilus influenzae* within airway epithelial cells and alveolar macrophages.[97] High-throughput sequencing of microbial 16S rRNA genes yields relatively unbiased estimates of the relative abundance of uncultivable and cultivable bacteria.[98,99] The lower airways of normal individuals harbor low levels of oral bacteria such as *Prevotella* spp. and *Veillonella* spp.[100,101] Culture-independent techniques have challenged the dogma that the lower airway is normally sterile and provide evidence that

there are residential organisms, especially in individuals with already damaged lungs. Oral anaerobes likely modulate the pulmonary immune response in health and disease. This possibility is supported by a growing body of data linking periodontitis, COPD exacerbations, and reduced lung function.[102] However, the technical challenges produced by contamination of lower airway samples with upper airway secretions needs to be resolved to better understand the role of airway microbiome in COPD pathogenesis.

Respiratory viruses are also frequently found in patients with stable COPD. Using culture or polymerase chain reaction (PCR) techniques to assess sputum, the most common respiratory virus is respiratory syncytial virus (RSV), which is found in up to 23.5% of COPD patients, followed by non-RSV viruses, such as rhinovirus, coronavirus, and parainfluenza virus, in 16.2% of samples.[103] Increased inflammation has also been reported with adenovirus.[104] High-throughput complementary DNA sequencing can identify viral transcripts in an unbiased approach. A fuller understanding of the role of the virome in stable COPD and in AECOPD awaits resolution of the technical challenges of high-coverage RNA sequencing in lower respiratory tract samples.

Microbes in Acute Exacerbations of COPD

Two thirds of patients with a COPD exacerbation have bacteria or viruses or both cultured from lower airway secretions. Aerobic bacteria are isolated in half of patients, respiratory viruses are isolated in one third, and bacterial/viral coinfection is present in a fourth of patients with acute exacerbations.[52,105] The increased incidence of AECOPD during the winter may reflect the significant role that viruses play in the pathogenesis of AECOPD.

H. influenzae, S. pneumoniae, and *M. catarrhalis* are the bacterial pathogens most commonly isolated during COPD exacerbations. The same three also colonize stable COPD patients, and higher bacterial loads have been associated with AECOPD.[52,94,95,106-109] In a series of studies using molecular biologic techniques, Sethi and associates have observed that acquisition of a new bacterial strain precedes AECOPD.[83,96,106,109,110] The increase in total bacterial load during a COPD exacerbation is relatively small compared with the total bacterial load.[109] In their model, the humoral and cellular immune responses to the new bacterial or viral strain likely drive the increased inflammation that causes the COPD exacerbation.

Individuals with greater degrees of functional impairment, recent antibiotic use, or systemic corticosteroid therapy have higher rates of isolation of gram-negative bacteria, such as *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and members of the Enterobacteriaceae, from sputum.[111,112] Patients with an FEV_1 greater than 35% of predicted value and no systemic corticosteroid or antibiotics within the preceding 3 months have a low probability of Enterobacteriaceae or *P. aeruginosa* in sputum culture.[112] *H. influenzae* and *P. aeruginosa* are more common in patients with poorer lung function.[108] Polymicrobial exacerbations occur with advanced pulmonary dysfunction and severe exacerbations.[105,113]

The role of "atypical" bacterial pathogens such as *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila* in exacerbation is poorly defined, but they are rarely found in AECOPD.[50,103,114] Variations in reported rates of atypical pathogens could be related to the technical or geographic differences between reports.[89,115] When serology or *M. pneumoniae* antigen detection has been used to indicate the presence of *M. pneumoniae* as a pathogen, PCR assay and culture frequently do not confirm its presence.[103,116,117] Alternately, two reports from Italy and Greece demonstrate *M. pneumoniae* among between 7% and 9% of patients with AECOPD using serologic and PCR techniques.[118,119] Controversy also exists regarding the role of *C. pneumoniae* in COPD exacerbations. Several well-conducted studies detected no *C. pneumoniae* or *L. pneumophila*,[103,117] whereas others detected *C. pneumoniae* in 6% to 9% of those with AECOPD.[89,118] Chronic colonization with *C. pneumoniae* occurred in one third of patients and was associated with worse pulmonary function in one study.[89]

Unlike stable COPD, rhinovirus is the virus most frequently associated with AECOPD.[103,105,120] Coronavirus, parainfluenza, adenovirus, influenza virus, and human metapneumovirus also occur but are less prevalent.[113,120] Coinfection with viruses and bacteria produce higher bacterial burden, more sputum eosinophils, greater lung function impairment, and longer hospitalization.[105,113] It is likely that viruses and bacteria induce independent inflammatory pathways, accounting for more severe presentations and poorer outcome of patients with coinfection.

NONANTIMICROBIAL THERAPY FOR STEADY-STATE COPD

Treatment of stable COPD should improve the patient's symptoms and functional status, reduce the risk for exacerbations, and slow the decline of lung function.[4] Smoking cessation and avoidance of environmental exposure are the most important interventions to prevent disease progression and should be encouraged at every medical visit. Multiple different behavioral and pharmacologic treatments should be explored, including varenicline, nicotine replacement, and bupropion.[121-124] Pneumococcal, influenza, and combined tetanus/diphtheria/acellular pertussis (Tdap) vaccination is also recommended for every COPD patient.[4,125]

β_2-Agonist and anticholinergic bronchodilators (usually long-acting formulations) are the mainstays of symptom control (Table 67-2).[4] These drugs relax airway smooth muscle, producing bronchodilation, and also have anti-inflammatory activity, although the clinical significance of this is not clear.[126] Anticholinergic medications also reduce sputum production in patients with chronic bronchitis. Corticosteroids in steady-state COPD are restricted to adjunctive therapy complementing long-acting bronchodilators in more severe cases of

TABLE 67-2 Modified Global Initiative for Chronic Lung Disease (GOLD) Treatment Recommendations According to Stable-State Patient-Group Category

PHARMACOLOGIC OPTIONS

Patient Group	First Choice	Second Choice	Alternative Choice
A FEV_1 >50% Mild symptoms ≤1/yr Exacerbations	SABA prn or SAMA prn	LABA or LAMA or SABA and SAMA	Theophylline
B FEV_1 >50% Moderate symptoms ≤1/yr Exacerbations	LABA or LAMA	LAMA and LABA	SABA and/or SAMA Theophylline
C FEV_1 ≤50% Mild symptoms ≤1/yr Exacerbations	ICS + LABA or LAMA	LAMA and LABA	PDE-4 inhibitor SABA and/or SAMA Theophylline
D FEV_1 ≤50% Moderate symptoms ≥1/yr Exacerbations	ICS + LABA or LAMA	ICS and LAMA or ICS + LABA and LAMA or ICS + LABA and PDE-4 inhibitor or LAMA and LABA or LAMA and PDE-4 inhibitor	Carbocysteine SABA and/or SAMA Theophylline Azithromycin

NONPHARMACOLOGIC TREATMENT OPTIONS

Patient Group	Essential	Recommended
A	Smoking cessation	Physical activity Influenza and pneumococcal vaccination; Tdap
B-D	Smoking cessation Pulmonary rehabilitation	Physical activity Influenza and pneumococcal vaccination; Tdap

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; PDE-4, phosphodiesterase-4; prn, as needed; SABA, short-acting β_2-adrenergic agonist; SAMA, short-acting muscarinic antagonist; Tdap, combined tetanus/diphtheria/pertussis vaccine.

Modified from Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. GOLD executive summary. Am J Crit Care Med. *2013;187:347-365.*

COPD. Inhaled corticosteroids do not reduce mortality but do reduce COPD exacerbations,[127] decrease inflammation, and stabilize lung function in moderate and severe COPD.[128] Unfortunately, inhaled corticosteroids increase the risk for pneumonia, which must be balanced with the benefit of less frequent exacerbations.[127,129] Other drugs, such as nonselective and selective phosphodiesterase inhibitors (e.g., theophylline and roflumilast, respectively), may also be considered in patients with severe COPD with frequent exacerbations that are not adequately controlled by long-acting bronchodilators.[130,131]

NONANTIMICROBIAL THERAPY FOR ACUTE EXACERBATIONS OF COPD

Systemic corticosteroids (either oral or intravenous) and bronchodilators (inhaled β_2-agonists with or without anticholinergics) are the cornerstones of pharmacologic treatment of AECOPD. Short-acting bronchodilators are preferred because they allow titration of the dose required and because there is no clinical trial that has evaluated the use of long-acting bronchodilators during AECOPD. Although for sicker patients nebulized bronchodilators are routinely used in the hospital, data suggest similar bronchodilator effects with metered-dose inhalers.[132] A 10- to 14-day course of systemic corticosteroids reduces treatment failure by 46% during both inpatient and outpatient management of COPD exacerbations.[133] Systemic corticosteroids are preferred during an exacerbation because they reduce recovery time, improve lung function, and increase arterial oxygenation.[134-138] Systemic corticosteroids also reduce the rate of early relapse and length of hospital stay. Although there are no data to support a specific dose or route of administration for corticosteroids, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend 30 to 40 mg of oral prednisolone per day for 10 to 14 days.[4,138-140]

ANTIBIOTIC THERAPY FOR ACUTE EXACERBATIONS OF COPD

Rationale for Antibiotics

Early antibiotic treatment of AECOPD in both the outpatient and inpatient settings has become nearly routine in clinical practice even though the role of bacteria in many cases of AECOPD is uncertain. The choice of antibiotic has changed during the past several decades, in part reflecting the changing resistance patterns of infecting bacteria as well as the availability of newer antibiotics that are taken less frequently, have improved antimicrobial activity, and are less toxic. Studies evaluating the effect of antibiotic treatment are mostly small and are difficult to compare because of heterogeneous patient populations, diverse outcome measures, and varied definitions of failure. Additionally, many different antibiotics and treatment durations have been evaluated, reducing comparability between individual studies. Two recent meta-analyses and a Cochrane review concluded that antibiotics improve outcome in AECOPD among inpatients, especially those requiring admission to an intensive care unit.[133,141,142] Among hospitalized patients, antibiotics reduced hospital mortality by 78%.[143,144,145] Antibiotics also led to improved peak expiratory flow by 22%.[141] The largest study to date evaluating antibiotic efficacy is a retrospective cohort of 84,621 inpatients from 413 acute care centers in the United States.[146] Administration of antibiotics within the first 48 hours reduced the need for mechanical ventilation after 2 hospital days (1.07% vs. 1.80%), lowered rates of inpatient mortality (1.04% vs. 1.59%), reduced readmissions (7.91% vs. 8.79%), and produced fewer treatment failures (9.77% vs. 11.75%). However, there was a higher rate of *Clostridium difficile* in patients who were treated with antibiotics (0.19% vs. 0.94%). The weight of evidence supports antibiotic use for hospitalized patients, particularly those admitted to the intensive care unit.

As opposed to relatively high-quality evidence supporting the use of antibiotics in the inpatient setting, there has been less convincing evidence to recommend antibiotics for outpatients. In the Cochrane review cited earlier, reduction in treatment failure was found when analyzing all outpatient studies but not found when the analysis was restricted to studies using currently available antibiotics.[37,142,147,148,149] However, a recent multicenter double-blind, placebo-controlled clinical trial of mild to moderate AECOPD documented that amoxicillin-clavulanate improves response to therapy within 9 to 11 days (74.1% vs. 59.9%) and increased the median time to the next exacerbation from 160 days in the placebo group to 233 days in those receiving antibiotic.[148] This study, which was published since the most recent meta-analysis, suggests that antibiotics may be beneficial for some patients with mild to moderate AECOPD. Several other studies have demonstrated a delayed time to relapse or exacerbation with the use of antibiotics to treat AECOPD. In a retrospective cohort outpatient study of 270 patient-visits (with relapse defined as a return visit within 14 days), antibiotics reduced the relapse rate to 19% (50/270) compared with 32% (29/92) among patients who did not receive antibiotics. Patients who received amoxicillin, however, had an even higher relapse rate of 54% (20/37) compared with those who did not receive antibiotics.[150] In another study, antibiotics added to oral corticosteroids increased the median time from second to third exacerbation from 189 days to 258 days and reduced mortality.[151] The limited effectiveness of antibiotics on less severe exacerbations may be a result of lower bacterial burden in this healthier group of patients.

Whom to Treat

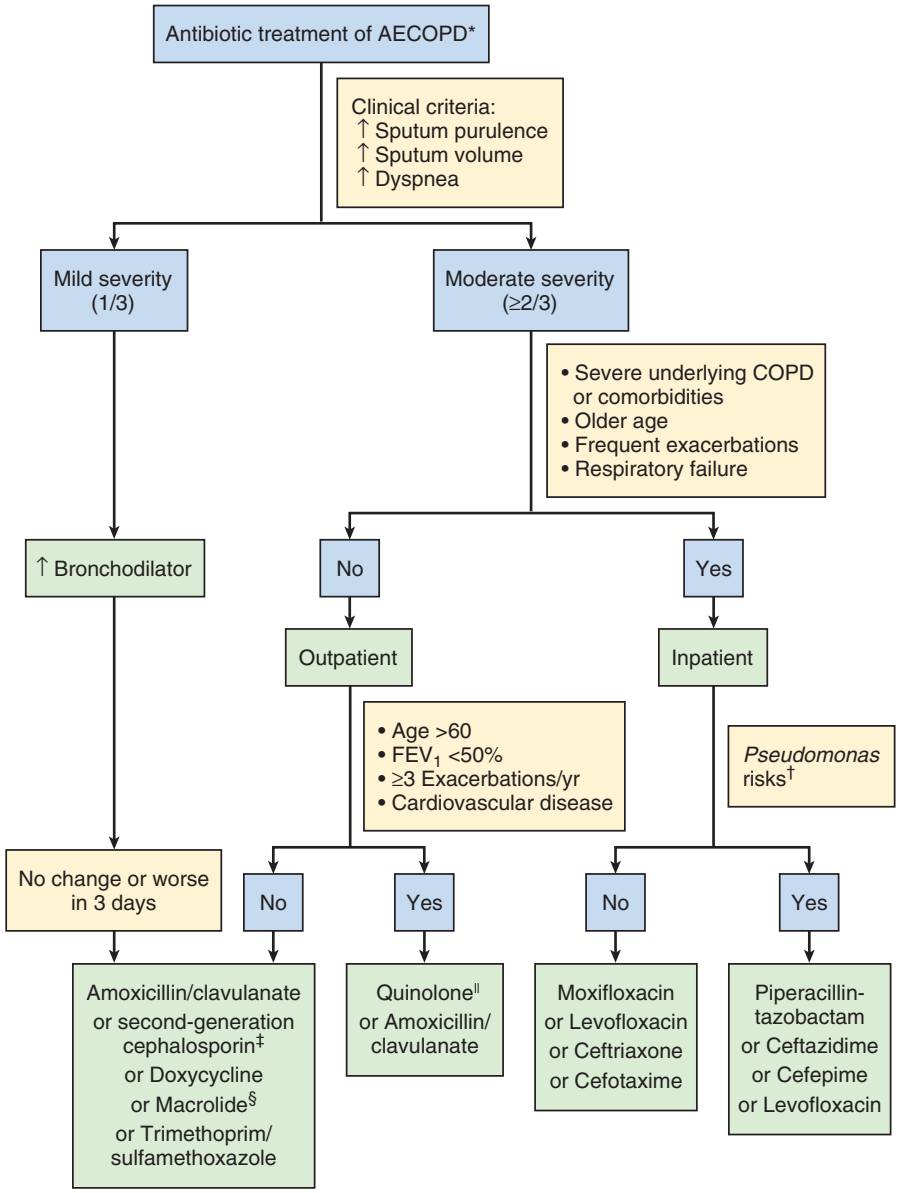
Given the large numbers of patients with COPD who develop AECOPD and the potential economic impact both in terms of antibiotic cost and toxicities of treatment, there has been much effort to identify patients who do not require antibiotics. Recent well-designed clinical investigations have used procalcitonin as a biomarker for bacterial infection in acute exacerbation in an attempt to limit unnecessary antibiotic use and reduce the emergence of antibiotic resistance and *C. difficile* infection.[152,153,154]

The authors of the GOLD guidelines recommend antibiotic therapy for patients who have AECOPD who meet one of the following criteria: (1) present with all three "cardinal" symptoms: increased dyspnea, increased sputum volume, and increased sputum purulence; (2) present with two of the cardinal symptoms if increased purulence of sputum is one of the two symptoms; (3) have a severe exacerbation that requires mechanical ventilation (invasive or noninvasive).[4]

In recent studies, patients who do not meet these criteria frequently are prescribed antibiotics. Studies involving outpatients and inpatients have demonstrated that although approximately 80% of patients receive antibiotics, purulent sputum is only found among only 39% to 64% of patients.[155-157] In a study from the United States, there was no correlation between the use of antibiotics and the presence of an indication for their use.[158] In a more recent study, 20% of patients who did not meet GOLD criteria for antibiotics received antibiotics before hospitalization whereas approximately 20% who met the criteria did not receive antibiotics.[159] Although the use of bacterial cultures for treatment of AECOPD is debated, the use of purulence to define the need for antibiotics is based on several studies demonstrating a relationship between sputum color and/or neutrophils and positive bacterial cultures.[160-163] Sputum purulence has been an excellent guide of antibiotic use in several studies. In one, if sputum purulence was not present and antibiotics withheld, only 2 of 32 patients failed therapy.[163] In another study in which purulence was used to determine whether antibiotics would be prescribed, the therapeutic failure rate was 9% among those who had nonpurulent sputum and did not receive antibiotics versus 10% among those with purulent sputum who received antibiotics.[164] It is clear that many patients are prescribed antibiotics who do not need them, but the current state of knowledge does not clearly define the group who will be harmed more than they will be helped by a course of antibiotics. The GOLD recommendation for using antibiotics is based on symptoms, in particular sputum purulence, which remains the best guide to decide which patients with AECOPD require antibiotics.

Choice of Antibiotic

Most recent comparative studies have employed noninferiority designs to demonstrate equivalency between antibiotics. Among the more commonly studied antibiotics are macrolides (azithromycin and clarithromycin), second-generation cephalosporins (cefuroxime, cefpodoxime, cefdinir), penicillin/penicillinase inhibitors (ampicillin/clavulanate), quinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin), trimethoprim-sulfamethoxazole, and tetracyclines (doxycycline). Most of these trials have been performed among



*If antibiotics used within past 3 months, use antibiotics from different class.
†*Pseudomonas* risk factors: >4 episodes antibiotics in past year, hospitalization within past 90 days, prior culture for *Pseudomonas*, FEV_1 <50% predicted.
‡cefpodoxime, cefuroxime, cefdinir.
§azithromycin, clarithromycin.
‖levofloxacin, moxifloxacin, gemifloxacin.

FIGURE 67-2 Flowchart for antibiotic treatment decision in chronic obstructive pulmonary disease (COPD) exacerbation. AECOPD, acute exacerbations of COPD; FEV_1, forced expiratory volume in 1 second.

patients with acute exacerbation of chronic bronchitis. Several meta-analyses have been performed evaluating randomized, controlled antibiotic comparison trials for treatment of AECOPD.[165-167] No agent or class is consistently superior in comparison to others using clinical endpoints, although in any single study one agent may appear superior in terms of microbiologic eradication of one bacterium or overall microbiologic eradication.[165,168,169] There may be higher relapse rates when AECOPD are treated with amoxicillin as compared with other antibiotics.[150] Increasing β-lactamase production by *S. pneumoniae, H. influenzae,* and *M. catarrhalis* challenges the use of amoxicillin or ampicillin as first-line treatment of AECOPD.[170,171] An evaluation of 19,608 patients who were treated with either a quinolone antibiotic (13,469 patients) or macrolide antibiotic (6,139 patients) taken from a larger retrospective cohort study of hospitalized patients with AECOPD showed similar rates of treatment success, although less diarrhea in the macrolide cohort.[172] Antimicrobial recommendations for the larger group of COPD patients with acute exacerbations are extrapolated from these data (Fig. 67-2).

Treatment is empirical and is based on risk factors for both antibiotic resistance and infection with Enterobacteriaceae or *P. aeruginosa* and to some extent dependent on the need for hospitalization (see Fig. 67-2). The specific choice of antibiotic should be made with an understanding of local bacterial resistance patterns, toxicity, allergies, drug interactions, and comorbidities. A sputum sample is not recommended routinely by either the GOLD guidelines or those of the American College of Physicians/American Society of Internal Medicine and the American College of Chest Physicians.[4,173] Sputum cultures and Gram stains are not reliable in terms of indicating the infecting pathogen. Furthermore, early sputum cultures do not seem to affect outcome with antibiotic treatment among inpatients.[146] An exception to this

recommendation should be considered for patients who have failed prior therapy and patients at high risk for infection due to Enterobacteriaceae or *P. aeruginosa.*

Patients with AECOPD generally do not present with significant systemic illness. By definition, chest radiographs do not demonstrate a new pulmonary infiltrate. Confusion is created because up to one fifth of patients hospitalized for community-acquired pneumonia have normal chest films on hospital admission but develop an infiltrate within 48 hours.[174] The combination of overlap between AECOPD and community-acquired pneumonia along with antibiotic resistance leads to frequent use of broad-spectrum antibiotics in many hospitalized patients with AECOPD.[158] If chest radiographs do not demonstrate an infiltrate at 48 hours, antibiotics can be tailored or stopped but still may be useful for AECOPD meeting other criteria.[175]

Despite increasing resistance to many of the older antibiotics, patients still respond to them clinically. Trimethoprim-sulfamethoxazole and ciprofloxacin were equally effective in a recent double-blind trial among patients with severe AECOPD requiring mechanical ventilation.[176] Surprisingly, bacterial susceptibility did not predict clinical success.[176] This may be due to the poor sensitivity and specificity of sputum samples in defining the bacteria that caused the acute exacerbation. Alternately, AECOPD may be driven by changes of a complex lower airway microbiome and not by a single microorganism. A shift in the lung microbiome could produce a flare of inflammation. Given the polymicrobial nature of the microbiome, organisms may not need to be effectively treated to reduce inflammation. In the near future, unbiased culture-independent techniques will more accurately describe the lung microbiome in COPD. A better understanding of microbiome changes preceding AECOPD and alterations produced by antibiotics will improve our understanding of the antibiotic response.

Duration of Antibiotic Therapy

Outpatient studies have compared duration of therapy in acute exacerbations of chronic bronchitis. Five days of therapy with a quinolone, second-generation cephalosporin, or macrolide is as efficacious as and associated with fewer adverse reactions than 7 days of antimicrobial therapy.[177-180] Although there are no comparable inpatient trials, durations of therapy have varied between 7 and 14 days; 10 days of treatment were used in recent studies of hospitalized patients with AECOPD.[144,176] If tolerated, oral therapy is as effective as intravenous antibiotics.[144] Eight days of therapy, which is currently recommended for ventilator-associated pneumonia, may suffice even in critically ill patients.[181]

Therapy for Viral Infection

Patients with COPD would be considered at high risk for severe influenza infection and should be offered neuraminidase inhibitors (e.g., oseltamivir or zanamivir) when they present with an influenza-like illness during influenza season, even in the setting of a negative rapid virus detection study.[182] Nonimmunized people with COPD who have had close family contact with a person with influenza should receive chemoprophylaxis with a neuraminidase inhibitor.[182]

Although numerous viruses other than influenza virus have been associated with AECOPD as noted earlier, currently there are no treatment options for these viruses. Although inhaled ribavirin has been used therapeutically for infants and transplant patients with severe RSV infection, studies are not available using this agent in patients with COPD. As diagnostic and therapeutic modalities improve, specific antiviral therapy may become part of the armamentarium to decrease the duration of a COPD exacerbation.

PREVENTION OF ACUTE EXACERBATIONS OF COPD

Antibiotic Prophylaxis in Steady-State COPD

Because bacterial colonization of lower airways plays a significant role in AECOPD, prophylactic use of antibiotics has been investigated. Successful use of prolonged, continuous oxytetracycline in a small number of patients was attempted in Great Britain as early as the mid-1950s.[183] The effectiveness of prophylaxis with oxytetracycline was not corroborated in later studies.[184,185] More recently, erythromycin, clarithromycin, and azithromycin have been the most widely studied prophylactic agents. Observational and placebo-controlled trials suggested long-term macrolide prophylaxis is effective in reducing exacerbations and hospitalizations.[186-189] A recent large-scale randomized, placebo-controlled study of azithromycin, 250 mg daily for 1 year, reduced AECOPD from 1.82 exacerbations per patient-year in the placebo group to 1.48 exacerbations per patient-year in the azithromycin group. Antibiotic treatment also extended time to first exacerbation from 174 to 266 days and improved quality of life.[189] The azithromycin group, however, had more hearing loss.[189] Among patients who became colonized, macrolide resistance occurred in 81% of the treated group versus 41% of the placebo control group. Importantly, this trial excluded patients with cardiovascular risks, including a resting heart rate greater than 100 beats per minute, prolonged QT (QTc) interval, or medications that increase the QTc interval. Therefore, the potential for adverse cardiac reactions reported with macrolides was minimized in this study. Controversy still exists about the increased risk for cardiovascular events reported with azithromycin use.[190,191] In addition, intermittent short courses of macrolides produced a fourfold increase in *S. pneumoniae* within 6 months.[192] The mechanisms that reduce exacerbation go beyond their antibacterial effect. These drugs are directly anti-inflammatory, decreasing proinflammatory cytokine production, adhesion molecules, and reactive oxygen species.[193,194] Long-term macrolides have also been studied in patients with cystic fibrosis and bronchiectasis in whom they have led to fewer exacerbations of disease and stabilization of lung function.[195,196] For patients with low cardiovascular risk and frequent exacerbation in spite of adequate routine therapy, macrolides should be considered (see Table 67-2). However, more widespread use of macrolides in less severe COPD cases is not currently recommended.

Another strategy to prevent AECOPD is intermittent antibiotic therapy. Moxifloxacin, 400 mg for 5 days every 8 weeks for a total of 6 courses, reduced the odds of exacerbation by 20% in the intention-to-treat analysis and by 45% among patients with baseline purulent sputum. The authors reported no increased resistance to moxifloxacin among cultured bacteria but did find more gastrointestinal problems (4.7% moxifloxacin vs. 0.7% placebo).[197] Further research is needed to confirm that benefits of this approach outweigh the risks for resistance and *C. difficile* colitis before this strategy gains widespread use.

Vaccination

The influenza, pneumococcus, and tetanus/diphtheria/acellular pertussis (Tdap) vaccines are recommended for patients with COPD. Influenza vaccination is recommended annually for persons with COPD by both the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP).[4,125,198] Observational studies have demonstrated both decreased hospitalizations and mortality among elderly individuals who received influenza vaccine.[199,200] However, data from randomized, placebo-controlled studies are less compelling.[201,202] Influenza vaccine significantly reduces AECOPD, with over 60% effectiveness, but has failed to demonstrate significant reductions in hospitalization or mortality.[201,202] The effectiveness of the influenza vaccine is not related to age, sex, severity of COPD, or comorbid illness. Despite the results of the placebo-controlled studies, given the lack of major toxicities, it is recommended for patients with COPD.

Pneumococcal vaccine is also recommended for all persons with COPD.[4,125] Pneumococcus is a common colonizing organism as well as pathogen in this population. Some observational studies have demonstrated a decrease in pneumococcal bacteremia in the elderly as well as hospitalization for pneumonia and mortality among elderly patients with chronic lung disease.[203,204] Others have not been able to corroborate these findings.[205] Randomized, placebo-controlled trials have frequently not found the pneumococcal vaccine to be very effective. A recent meta-analysis included seven studies, of which two used the 14-valent vaccine and five the 23-valent vaccine.[206] The authors reported that there was no reduction in the likelihood of developing pneumonia nor in preventing AECOPD among patients who received the vaccine compared with those who did not.[206] Other analyses in this Cochrane review did not demonstrate a decrease in all-cause mortality or death from cardiorespiratory causes. There are no published data

regarding the use of the 13-valent conjugate vaccine, which provides better coverage. A recent study has demonstrated decreased hospitalization rates after introduction of the 7-valent pneumococcal vaccines that were most marked in the very young and elderly, although present in all age groups. Although this may hold true for patients with a history of COPD, the data did not stratify patients by underlying disease or risk factors.[207]

Several studies have reported that there is an additive effect using both the influenza vaccine and pneumococcal vaccine among patients with COPD. There was a significant reduction in hospitalization (63%) as well as mortality (81%) when both vaccines were administered compared with no vaccine.[208] Two more recent cohort studies from Japan have demonstrated better outcomes when both influenza vaccine and pneumococcal vaccines were administered compared with influenza vaccine alone.[209,210]

Although there are no studies regarding efficacy of Tdap among patients with COPD, serologic diagnosis in Switzerland has reported *Bordetella pertussis* in a significant portion of patients with AECOPD.[211] However, all cultures and PCR assays for *Bordetella* spp. were negative in this study. Therefore, it is not certain how to interpret the serologic data. Tdap is recommended by the CDC and ACIP for all adults of ages 19 to 64 years, and patients with COPD should receive this vaccine, particularly in light of the recent surge in cases of pertussis reported among adults.[125]

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