Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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- Chronic obstructive pulmonary disease (COPD) is characterized by **airway inflammation and parenchymal destruction.**

- **increasing dyspnea and sputum production**; these are the essence of the diagnosis of acute exacerbation of chronic obstructive pulmonary disease (**AECOPD)**

- Once AECOPD is established, its management includes a combination of **antibiotics and steroids**.

EPIDEMIOLOGY

- COPD, including emphysema and chronic bronchitis, has been the third leading cause of death since 2008 in the United States.
- the **third leading cause of death in the world by 2020.**
- **By 2030, 10%** of the world's population will be expected to **develop COPD**
- **50%** of smokers will develop COPD
- COPD is caused by multiple factors, including **environmental exposures, infections, inflammation, and genetic predisposition**
- Newer conceptualization of COPD characterizes it as a **syndrome that includes multiple different processes with distinct pathophysiologic derangements**

Risk factors

- Tobacco smoking
- occupational dust exposures,
- outdoor air pollution,
- poor indoor air quality from burning biomass fuels
- Immunoglobulin A (IgA)-deficient
- Human immunodeficiency virus (HIV)
- Genetic susceptibility(Mutation of the a1-antitrypsin gene) Homozygous a1-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
- Poor socioeconomic status, chronic asthma, intrauterine growth retardation,poor nourishment, and history of pulmonary tuberculosis are other risk factors for COPD

DIAGNOSIS

- COPD is characterized by progressive airflow obstruction defined by reduction in forced expiratory volume in 1 second (FEV1) and a postbronchodilator ratio of FEV1/forced vital capacity (FVC) less than 70% on pulmonary function tests (PFTs)

TABLE 66.1 Spirometric General Classification of Chronic Obstructive Pulmonary Disease (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	50–79
GOLD 3: Severe COPD	≤0.7	30–49
GOLD 4: Very severe COPD	≤0.7	<30

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

- AECOPD produces significant morbidity and mortality
- **two or more exacerbations per year** = **COPD with poor outcome**
- Risk factors include viral and bacterial infections, change in environmental conditions such as smog, gastroesophageal reflux, lack of compliance with maintenance treatment, and severity of baseline disease, winter

CLINICAL PRESENTATION

- AECOPD manifests with progressive shortness of breath, cough, sputum production, reduced energy, and exercise limitation
- **Worsening symptoms, increased sputum volume, and transition of sputum color from clear to green or yellow suggest AECOPD**, which more commonly occurs during winter months
- Although there is no universal agreement on how to define or diagnose AECOPD, it is commonly defined as an acute event with worsening respiratory symptoms beyond normal day-to-day variation. The definition often requires increased rescue β-agonist inhaler use or addition of a long-acting muscarinic antagonist (LAMA) to control symptoms

- The main differential diagnosis of exacerbations in patients with COPD **includes pneumonia and congestive heart failure ,acute coronary syndrome, pulmonary embolism,**
- Other chronic pulmonary diseases with similar clinical presentation and acute exacerbations should be differentiated from COPD because treatment differs. Examples of these include **asthma, cystic fibrosis, bronchiectasis, diffuse panbronchiolitis, and obliterative bronchiolitis**

Diagnose the presence and severity of AECOPD requires patients to have at least one of the following clinical presentations:

- upper respiratory infection symptoms within the prior 7 days,
- Increased wheezing, fever without another identified cause, or
- an increase in heart rate or respiratory rate >20% from baseline.
- This scale then categorizes patients into three groups based on whether they have worsening dyspnea, increase in sputum purulence, increase in sputum volume, or a combination of these.

- A severe exacerbation meets all three criteria,
- a moderate exacerbation meets two,
- mild exacerbation meets only one
- procalcitonin is a biomarker that may be useful in determining the need for antibiotics

Risk factors associated with COPD exacerbations include:

- Having two or more COPD exacerbations in the previous year,
- reduced FEV1,
- smoking,
- and nonadherence with O2 therapy

The risk of sever exacerbation depends on:

each patient's **medical history**, including,

baseline FEV1

- number of prior exacacerbations,
- prior need for mechanical ventilation,
- and comorbidities.

the presence of severe exacerbation should prompt consideration

To hospital admission

- **Tachypnea** (especially with a respiratory rate above 25), **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.
- **arterial blood gas measurement** is more useful than oximetry because only the former can enable diagnosis of hypoventilation with hypercapnia.
- 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 (ICU) with noninvasive or invasive positive pressure ventilation

Additional diagnostic tests include

- chest radiography to identify pulmonary infiltrates
- electrocardiography to assess for cardiac ischemia and arrhythmias, particularly paroxysmal atrial tachycardia.
- The basic metabolic panel is helpful to assess severity of AECOPD.
- Elevated bicarbonate is a sign of chronic hypercapnia.
- Increased anion gap is a sign of anaerobic metabolism of the respiratory muscles, sepsis syndrome, or both.
- Hyponatremia sometimes occurs as a result of the syndrome of inappropriate antidiuretic hormone secretion.
- Hyperglycemia is a response to stress or systemic steroids,
- renal insufficiency is a manifestation of reduced cardiac output in end-stage pulmonary hypertension.

Radiology

- it is the **usual first step** in the evaluation of patients with progressive dyspnea and cough
- It is essential for evaluation of **alternative diagnoses** such as pneumonia, congestive heart failure, lung cancer, or pulmonary fibrosis.
- computed tomography (CT) is more sensitive for defining alternate diagnoses
- a helical CT scan with contrast can reveal Pulmonary emboli

PATHOPHYSIOLOGY

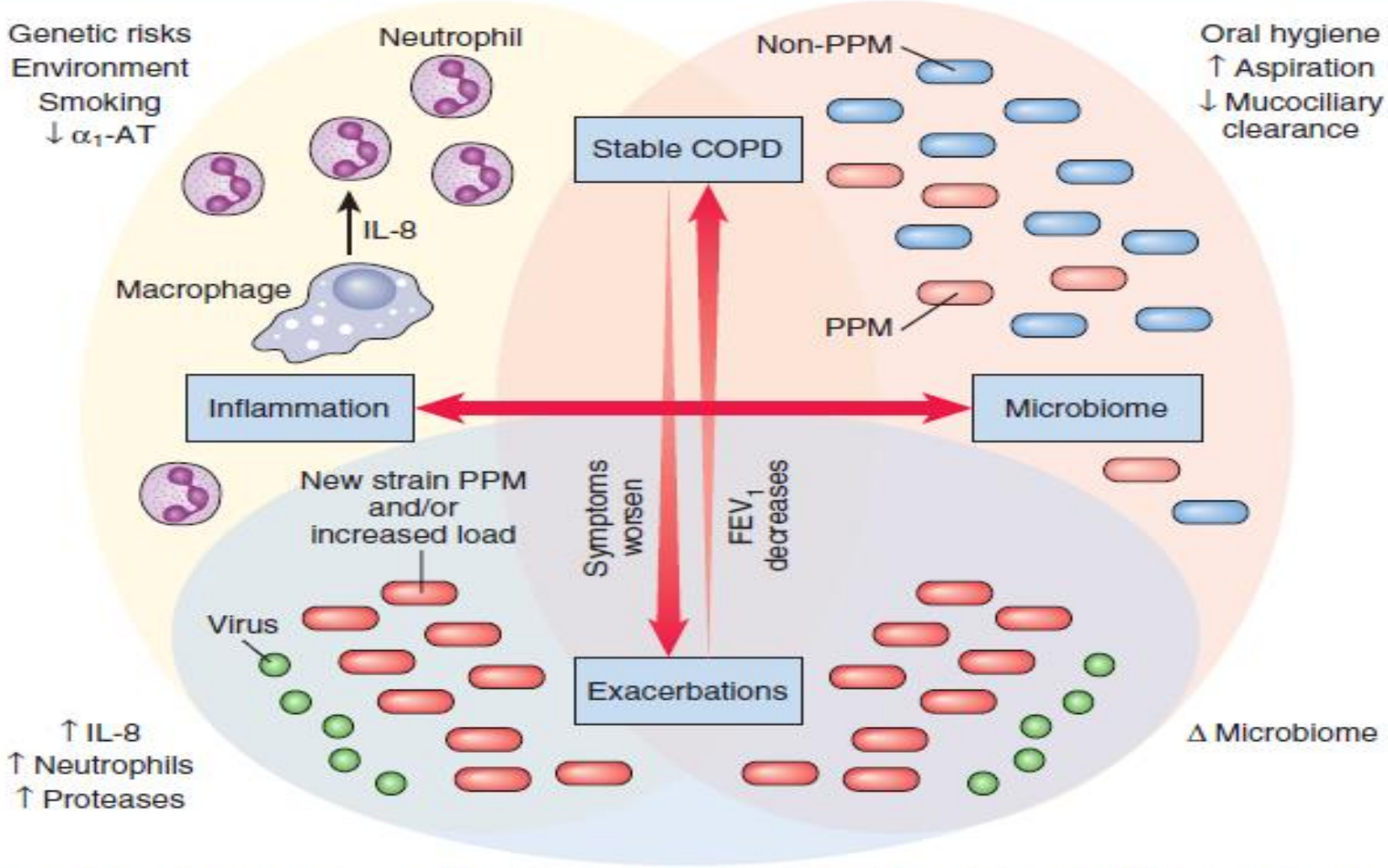


FIG. 66.1 Chronic obstructive pulmonary disease *(COPD)* pathophysiology. α_1-*AT,* α_1-Antitrypsin; *FEV_1,* forced expiratory volume in 1 second; *IL-8,* interleukin-8; *PPM,* potentially pathogenic microorganism.

Microbes in Stable Chronic Obstructive Pulmonary Disease

- **Increased bacterial colonization** of the lower airways in COPD occurs as a result of **chronic microaspiration, impaired clearance of bacteria, and frequent COPD exacerbations**
- **impaired mucociliary clearance in smokers** reduces the ability to clear oral microbes from the lower airways,
- Inhaled medications may also carry oral bacteria into the lower airway
- In stable COPD, the rates of positive routine bacterial cultures of sputum vary **between 22% and 83%**
- In stable COPD,non–potential pathogenic microorganisms (non-PPMs) are isolated much more frequently than potential pathogenic microorganisms(PPMs).

- **Non-PPMs** are usually oropharyngeal microbes such as ***Corynebacterium* spp.**, ***Neisseria* spp.**, ***Enterococcus* spp.**, **coagulasenegative staphylococci**, **viridans-group streptococci**, **and fungi such as *Candida* spp**
- **PPMs** are ***Streptococcus pneumoniae***, ***Haemophilus influenzae***, **and *Moraxella catarrhalis***
- respiratorysyncytial virus **(RSV)**, found in up to 23.5% of patients with COPD, followed by non-RSV viruses, such **as rhinovirus, coronavirus, and parainfluenza virus**, in 16.2% of samples.

Microbes in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

- ***H. influenzae, S. pneumoniae,* and *M. catarrhalis*** are the bacterial pathogens most commonly isolated during COPD exacerbations
- greater degrees of functional impairment, recent antibiotic use, or systemic steroid therapy have higher rates of isolationof gram-negative bacteria such **as *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and members of the Enterobacteriace ae family** from sputum.
- Patients with an FEV1 > 35% of predicted value and no systemic steroid or antibiotic use within the preceding 3 months have a low probability of Enterobacteriaceae or *P. aeruginosa* in sputum culture
- ***H. influenzae* and *P. aeruginosa*** are more common in patients with **poorer lung function**

- 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
- **Rhinovirus** is the virus frequently associated with AECOPD and is present approximately 20% to 34% of the time. **Coronavirus, parainfluenza virus, adenovirus, influenza virus, and human metapneumovirus** also occur but are less prevalent

TREATMENT

- **Nonantimicrobial Treatment of Steady-State Chronic Obstructive Pulmonary Disease:**
- Treatment of stable COPD should improve the patient's symptoms and functional status, reduce the risk of exacerbations, and slow the decline of lung function
- **Smoking cessation and avoidance of environmental exposure**
- **Pneumococcal, influenza, and combined tetanus, diphtheria, and acellular pertussis (Tdap) vaccination** is also recommended in every COPD patient

Nonantimicrobial Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

- Systemic corticosteroids (either oral or intravenous) and bronchodilatorsare the cornerstones of pharmacologic treatment of AECOPD
- GOLD guidelines recommend 30 to 40 mg of oral prednisolone per day for **10- to 14-day** reduces treatment failure by 46% during both inpatient and outpatient management of COPD exacerbations
- **they reduce recovery time, improve lung function, and increase arterial oxygenation also reduce the rate of early relapse and length of hospital stay**

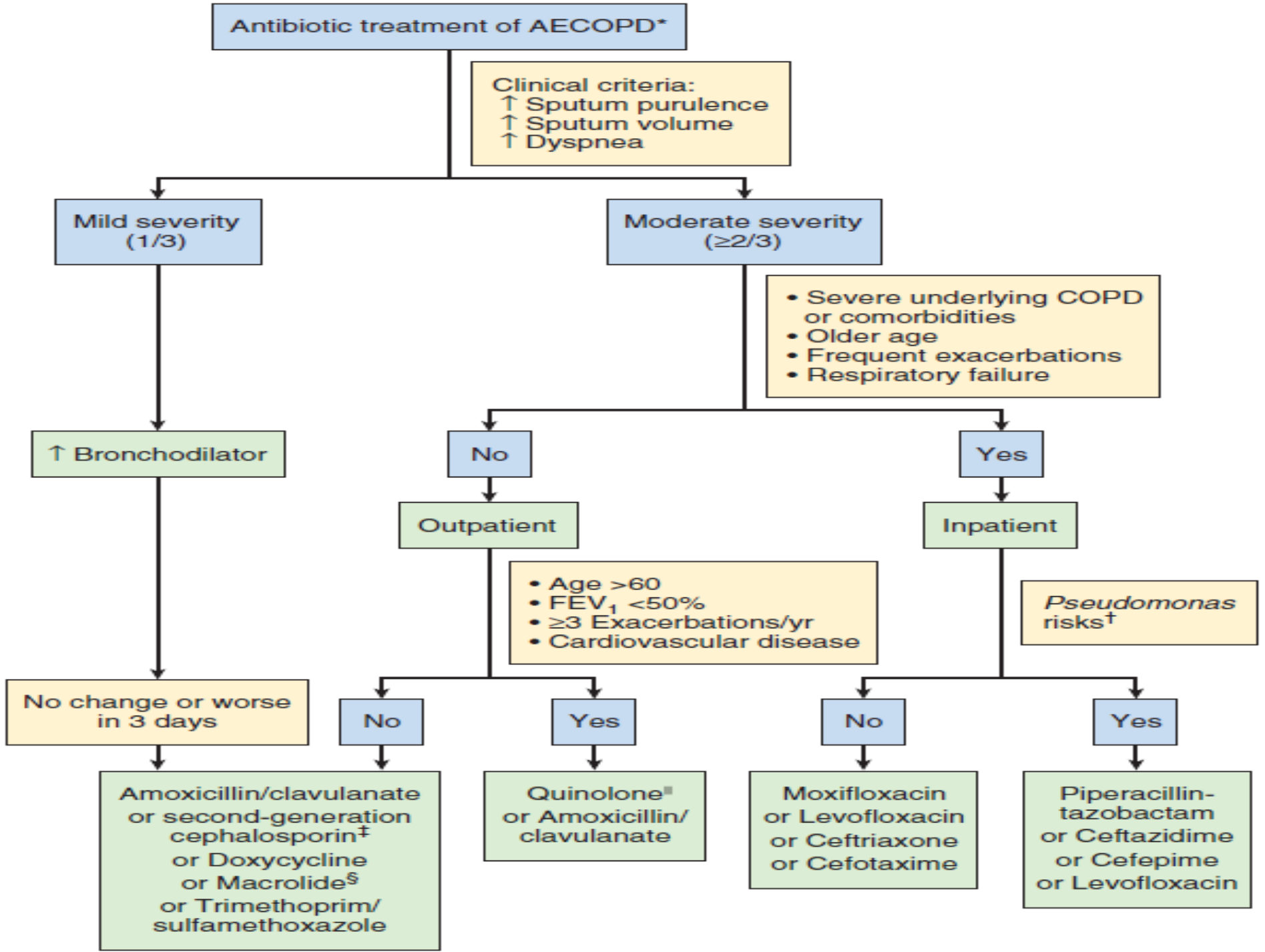
Antibiotic Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

- The authors of the GOLD guidelines note that treatment with antibiotics is controversial but recommend antibiotic therapy for patients who have AECOPD who meet one of the following criteria:
- (1) have all three "cardinal" symptoms—increased dyspnea, increased sputum volume, and increased sputum purulence;
- (2) have two of the cardinal symptoms if increased purulence of sputum is one of the two symptoms;
- (3) have severe exacerbation that requires mechanical ventilation (invasive or noninvasive)

Choice of Antibiotic

- 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** in either the GOLD guidelines or those of the American College of Physicians–American Society of Internal Medicine and the American College of Chest Physicians
- An exception to this recommendation should be considered for patients in whom prior therapy has failed and patients at high risk for infection due to Enterobacteriaceae or *P.aeruginosa*.

- Despite increasing resistance to many of the older antibiotics, patients still respond to them clinically
- Surprisingly,bacterial susceptibility did not predict clinical success.
- This may be due to the poor sensitivity and specificity of sputum samples in defining the bacteria that caused the AECOPD.


Antibiotic treatment of AECOPD*
Clinical criteria:
↑ Sputum purulence
↑ Sputum volume
↑ Dyspnea
Mild severity (1/3)
Moderate severity (≥2/3)
• Severe underlying COPD or comorbidities
• Older age
• Frequent exacerbations
• Respiratory failure
↑ Bronchodilator
No
Yes
Outpatient
Inpatient
• Age >60
• FEV1 <50%
• ≥3 Exacerbations/yr
• Cardiovascular disease
Pseudomonas risks†
No change or worse in 3 days
No
Yes
No
Yes
Amoxicillin/clavulanate or second-generation cephalosporin‡ or Doxycycline or Macrolide§ or Trimethoprim/ sulfamethoxazole
Quinolone or Amoxicillin/ clavulanate
Moxifloxacin or Levofloxacin or Ceftriaxone or Cefotaxime
Piperacillin-tazobactam or Ceftazidime or Cefepime or Levofloxacin

- *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*,
- FEV1 <50% predicted

- Although nebulized antibiotics have been used for the treatment and prevention of exacerbations in cystic fibrosis and bronchiectasis, there are **limited published reports evaluating the efficacy of inhalational antibiotics for the treatment of AECOPD**
- prolonged use of nebulized therapy may lead to microbial resistance.
- Nebulized amoxicillin-clavulanate for patients with COPD also has been shown to achieve adequate sputum concentrations and to have a good safety

Duration of Antibiotic Treatment

- Outpatient ;The GOLD guidelines currently recommend **5 to 7 days** of therapy.
- Although there are no comparable inpatient trials, durations of therapy have **varied between 7 and 14 days**

Treatment of Viral Infection

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

PREVENTIONS OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

- The goal of therapy is to avoid acute exacerbations because these are associated with accelerated declines in lung function
- β2-Agonists(long-acting β2-agonists [LABAs]) and
- anticholinergic bronchodilators(LAMAs) frequently combined in a single inhaler are effective in reducing exacerbations
- Oral phosphodiesterase inhibitors (e.g., theophylline and roflumilast, respectively) reduce the frequency of acute exacerbations, may also be considered in cases of severe COPD with frequent exacerbations that are not adequately controlled with long-acting bronchodilatorsalso

- Corticosteroids in steady-state COPD are restricted to adjunctive therapy complementing long-acting bronchodilators in **more severe cases of COPD** and may be most effective in patients with characteristics of **both COPD and asthma**. Inhaled corticosteroids do not reduce mortality but do reduce COPD exacerbations, decrease inflammation, and stabilize lung function in moderate and severe COPD
- Unfortunately, **inhaled corticosteroids increase the risk for pneumonia, which must be balanced with the benefit of less frequent exacerbation**

Antibiotic Prophylaxis in Steady-State Chronic Obstructive Pulmonary Disease

- long-term macrolide prophylaxis is effective in reducing exacerbations and hospitalizations
- intermittent short courses of macrolides produced a fourfold increase in *S. pneumoniae* within 6 months
- The mechanisms that reduce exacerbation go beyond their antibacterial effect. These drugs are directly antiinflammatory, decreasing proinflammatory cytokine production, adhesion molecules, and reactive oxygen species
- For patients with low cardiovascular risk **and frequent exacerbation in spite of adequate routine therapy, macrolides should be considered**
- Intermittent (thrice-weekly) and daily azithromycin appear to provide similar benefits

- Moxifloxacin 400 mg for 5 days every 8 weeks for a total of six courses reduced the odds of exacerbation by 20% in the intentionto- treat analysis of the enrolled COPD patients and by 45% among patients with baseline purulent sputum
- Further research is needed to confirm that the benefits of this approach outweigh the risks of resistance and C. *difficile* colitis before this strategy gains widespread use

TABLE 66.2 Modified GOLD Treatment Recommendations According to Stable State Patient Group Category

PATIENT GROUP	FIRST CHOICE	SECOND CHOICE	ALTERNATIVE C
Pharmacologic Treatment Options			
A	SABA prn	LABA or LAMA	Theophylline
Symptoms low	or	or	
Exacerbation: 0 or 1 (not leading to hospital admission)	SAMA prn	SABA and SAMA	
B	LABA	LAMA and LABA	SABA and/or SAMA
Symptoms high	or		Theophylline
Exacerbation: 0 or 1 (not leading to hospital admission)	LAMA		
C	LAMA	LABA and ICS	PDE4 inhibitor
Symptoms low	or LAMA and LABA		SABA and/or SAMA
Exacerbation: ≥2 or ≥1 leading to hospital admission			Theophylline
D	LAMA and LABA	ICS and LAMA	Carbocysteine
Symptoms high	or LAMA and LABA and ICS	or ICS and LABA and LAMA	Roflumilast
Exacerbation: ≥2 or ≥1 leading to hospital admission		or ICS and LABA and PDE-4 inhibitor or LAMA and LABA or LAMA and PDE-4 inhibitor	Theophylline Azithromycin

PATIENT GROUP	ESSENTIAL	RECOMMENDED
Nonpharmacologic Treatment Options		
A	Smoking cessation	Physical activity Influenza and pneumococcal vaccination; Tdap
B–D	Smoking cessation Pulmonary rehabilitation	Physical activity Influenza and pneumococcal vaccination; Tdap

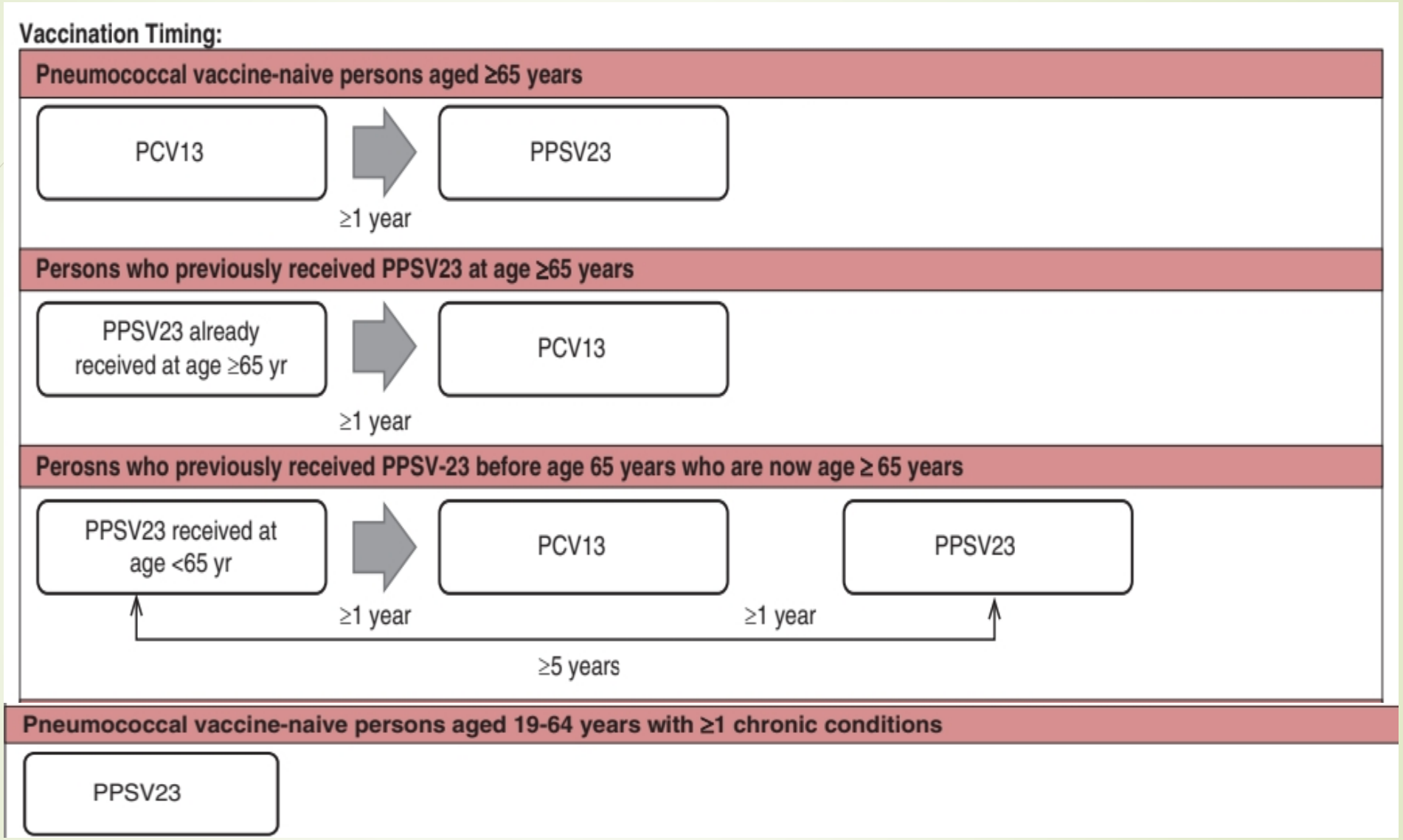
Symptoms low = mMRC 0–1 or CAT <10. Symptoms high = mMRC ≥2 or CAT ≥10.

CAT, COPD Assessment Test; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease criteria; *mMRC*, modified British Medical Research Council questionnaire; *ICS*,

Vaccination

- vaccines are recommended for patients with COPD:

- **influenza**,
- **pneumococcus**, The pneumococcal polysaccharide vaccine23 (PPSV23) and the pneumococcal conjugate vaccine 13 (PCV13) are both recommended for patients older than 65 years and the PPSV23 is recommended for those younger than 65 with COPD
- **Tdap**
- **Zoster vaccine** shouldbe administered to patients with COPD per current ACIP guidelines. High rates of herpes zoster infection, due to either immune alterations or frequent steroid use, have been reported in patients with COPD.


Vaccination Timing:
Pneumococcal vaccine-naive persons aged ≥65 years
PCV13
≥1 year
PPSV23
Persons who previously received PPSV23 at age ≥65 years
PPSV23 already received at age ≥65 yr
≥1 year
PCV13
Perosns who previously received PPSV-23 before age 65 years who are now age ≥ 65 years
PPSV23 received at age <65 yr
≥1 year
PCV13
≥1 year
PPSV23
≥5 years
Pneumococcal vaccine-naive persons aged 19-64 years with ≥1 chronic conditions
PPSV23

THANKS YOUR ATTENTION