COPD exacerbations: Clinical manifestations and evaluation

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INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a report produced by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO), defines an exacerbation of chronic obstructive pulmonary disease (COPD) as "an event characterized by dyspnea and/or cough and sputum that worsens over ≤14 days, which may be accompanied by tachypnea and/or tachycardia, and is often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways" [1,2]. This generally includes an acute change in one or more of the following cardinal symptoms:

- Cough increases in frequency and severity
- Sputum production increases in volume and/or changes character
- Dyspnea increases

The clinical manifestations and evaluation of patients with exacerbations of COPD are discussed in detail here. A table to assist with emergency management of severe acute exacerbations of COPD is provided (table 1). The diagnosis and treatment of stable COPD and the treatment, risk factors, prognosis, and prevention of exacerbations of COPD are discussed separately.

- (See "Chronic obstructive pulmonary disease: Diagnosis and staging".)

- (See "Stable COPD: Overview of management".)
- (See "COPD exacerbations: Management".)
- (See "COPD exacerbations: Prognosis, discharge planning, and prevention".)

EPIDEMIOLOGY

Among patients with COPD, the frequency of exacerbation varies with the severity of disease, and some patients have more frequent exacerbations than others independent of other measures of disease severity [1,3].

- Among almost 100,000 patients with COPD, the number of exacerbations in a baseline year of observation predicted the rate over the subsequent 10 years [4]. Approximately, 25 percent did not have an exacerbation; those with one baseline exacerbation were likely to have another (hazard ratio [HR] 1.71, 95% CI 1.66-1.77); and those with ≥5 events were even more likely to have future events (HR 3.41, 95% CI 3.27-3.56).

- A study of Medicare beneficiaries found a 64 percent readmission rate after a discharge for a COPD exacerbation [5].

- In a survey that included over 4000 respondents with COPD, approximately 10 to 25 percent needed an emergency room evaluation for COPD and 5 to 10 percent required hospitalization [6].

- In a separate survey of more than 1000 patients, 21 percent of those who reported a COPD exacerbation required hospitalization [7].

RISK FACTORS AND TRIGGERS

Risk factors — According to observational studies, the risk of developing an exacerbation of COPD correlates with the following features [8-19]:

- Advanced age
- Productive cough
- Longer duration of COPD
- History of antibiotic therapy
- COPD-related hospitalization within the previous year
- Chronic mucous hypersecretion
- Peripheral blood eosinophil count >0.3^4 x 10^9 cells/L (340 cells/microL)

- Theophylline therapy
- Use of medications leading to sedation or respiratory depression (including opioids, benzodiazepines, non-benzodiazepine hypnotics, and gabapentinoids)
- Presence of one or more comorbidities (eg, ischemic heart disease, heart failure, or diabetes mellitus)

Women are slightly more likely to experience a COPD exacerbation than men [13,20]. In general, worsening airflow limitation (lower forced expiratory volume in one second [FEV_1]) is associated with an increasing risk of COPD exacerbation, although airflow limitation alone does not provide a good assessment of exacerbation risk [1].

Other potential contributors to an increased risk of exacerbations include the following:

- **Severity of COPD and history of prior exacerbations** – The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest using primarily history of exacerbations, history of hospitalization for exacerbation, and symptoms to assess the exacerbation risk [1]. The number of exacerbations in the previous 12 months is stratified: a history of zero or one exacerbation suggests a low future risk of exacerbations, while two or more suggest a high future risk [1]. Symptoms (based on instruments such as the COPD Assessment Test [CAT] and the modified Medical Research Council Dyspnea Scale) further divide patients at low-risk into separate categories for more individualized pharmacologic management (algorithm 1).

  In the prospective Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, 2138 patients with moderate to severe airflow limitation (forced expiratory volume in one second [FEV_1] <80 percent predicted) were followed for three years [21]. The single best predictor of exacerbations was a history of prior exacerbations, regardless of severity of airway obstruction [4].

  Worsening airflow obstruction remains associated with an increasing prevalence of exacerbations, hospitalization, and death [22]. It is used as a component of the BODE index, a prognostic tool that can also be used to assess therapeutic response to medications, pulmonary rehabilitation therapy, and other interventions [23].

  Different COPD staging systems and severity assessments are discussed in more detail separately. (See "Chronic obstructive pulmonary disease: Diagnosis and staging", section on 'Assessment of severity and staging'.)

- **Gastroesophageal reflux disease** – Gastroesophageal reflux disease (GERD) may be an additional risk factor for COPD exacerbations [24,25]. In the ECLIPSE study noted above,

the occurrence of two or more exacerbations in a year was associated with a history of GERD or heartburn [21]. A similar observation was made in a case-control study that assessed the presence of GERD symptoms and frequency of COPD exacerbations in 80 patients with COPD. The presence of GERD symptoms was associated with an increased risk of COPD exacerbations (RR 6.55, 95% CI 1.86-23.11) [24]. However, in an observational study of 638 patients with stable COPD, therapy with proton pump inhibitors did not decrease the risk for severe exacerbations [26]. Additional studies are needed to determine whether GERD contributes to the development of COPD exacerbations.

- **Left ventricular diastolic dysfunction** – Left ventricular diastolic dysfunction at baseline is associated with a higher frequency of hospitalization for COPD exacerbation [27]. Diastolic dysfunction is common in patients with COPD, likely due to both comorbid vascular mechanisms (eg, hypertension, coronary artery disease, systemic inflammation) as well as metabolic and structural consequences of COPD (eg, lung hyperinflation, chronic hypoxia, and hypercapnia) [28,29]. Many of these contributing factors worsen during an exacerbation and may lead to diastolic decompensation, followed by pulmonary congestion and bronchial hyper-reactivity [30]. High heart rates, whether due to breathlessness, anxiety, or atrial arrhythmias, further exacerbate this pathophysiology.

- **Pulmonary hypertension** – Secondary pulmonary hypertension may be an additional risk factor for COPD exacerbations, possibly as an indicator of disease severity. In a follow-up to the ECLIPSE study, chest computed tomography scans were used to compute the ratio of the diameter of the pulmonary artery to the diameter of the aorta (PA:A ratio) [31]. In the study, a PA:A ratio greater than 1 was an independent risk factor for a future severe exacerbation (OR 3.44, 95% CI 2.78-4.25). Notably, a PA:A ratio >1 suggests the presence of pulmonary hypertension, although it does not clarify the cause of pulmonary hypertension (eg, hypoxemia due to COPD or other lung disease, left heart failure, sleep apnea). The clinical usefulness of this observation in terms of treatment decisions is unclear.

Triggers — Respiratory infections, most commonly viral (eg, rhinovirus) or bacterial, are estimated to trigger approximately 70 percent of COPD exacerbations (table 2) [1,32]; atypical bacteria are a relatively uncommon cause [33,34]. The remaining 30 percent are due to environmental pollution, pulmonary embolism, or have an unknown etiology [1,35-37]. (See "Management of infection in exacerbations of chronic obstructive pulmonary disease".)

COPD exacerbations have been associated with exposure to poor outdoor air quality, such as higher levels of ozone, carbon monoxide, particulate matter (up to 10 microns), and nitrogen dioxide [38,39]. Increased ambient levels of fine particulate matter (≤2.5 microns, aka $PM_{2.5}$) are

associated with an increase in hospitalization and mortality in COPD [40]. In a trial of 116 patients with COPD and exposure to poor air quality at home ($PM_{2.5}$ >10 mcg/m^3), use of indoor air filters versus sham air filters resulted in a dose-dependent improvement in respiratory symptoms and risk of moderate exacerbations [41].

As dyspnea and cough are nonspecific symptoms, COPD exacerbations of unknown etiology may be triggered or caused by other medical conditions, such as myocardial ischemia, heart failure, aspiration, or pulmonary embolism [1,42].

The relationship between COPD exacerbation and pulmonary embolism is illustrated by a prospective multicenter study of 1580 patients with COPD who were admitted to the hospital with acute worsening of respiratory symptoms [43]. Pulmonary embolism was identified in 266 (17 percent) when all patients were screened with CT of the pulmonary arteries (CTPA); 166 patients (11 percent) had pulmonary embolism involving the main or lobar pulmonary arteries. The presence of new purulent sputum reduced the odds of pulmonary embolism. Although the frequency of pulmonary embolism among patients hospitalized with an exacerbation of COPD varies across studies [44-47], a systematic review prior to this multicenter study showed a similar pooled prevalence of 23 percent when all patients were evaluated by CTPA within 48 hours of hospital admission (seven studies, 999 patients) [48]. An important limitation of these studies is their inability to determine whether the pulmonary embolism is the cause of the COPD exacerbation, a result of the COPD exacerbation, or a mere bystander.

CLINICAL MANIFESTATIONS

The clinical manifestations of exacerbations of COPD range from a mild increase in dyspnea, cough that is productive or nonproductive to respiratory failure with acute respiratory acidosis and/or hypoxemia.

Medical history — By definition, patients present with the acute onset or worsening of respiratory symptoms, such as dyspnea, cough, and/or sputum production, over several hours to days [1,49]. These symptoms should be characterized further in terms of the following features:

- Time course of the symptoms
- Comparison to baseline level of symptoms
- Severity of respiratory compromise (eg, dyspnea at rest, dyspnea climbing stairs, dyspnea severity using a visual analog [1-10] scale)
- Delineation of sputum characteristics (eg, amount, color, purulence, blood)

- Use of home oxygen now or in the past

Associated features that might suggest an alternate diagnosis or comorbidity include:

- Constitutional symptoms (eg, fever, chills, night sweats)
- Chest pain, chest pressure, peripheral edema, or palpitations
- Risk factors for coronary disease
- Risk factors for thromboembolic disease
- Upper respiratory symptoms that might suggest a viral respiratory infection or exposure to anyone with influenza

Patients should be asked if they currently smoke cigarettes or use vaping products. The past history of exacerbations should be ascertained: number of prior exacerbations, courses of systemic glucocorticoids, antibiotic therapy in the preceding three months, prior exacerbations requiring hospitalization or ventilatory support, and response to therapy of previous exacerbations.

Physical examination — Physical findings associated with an exacerbation of COPD often include wheezing and tachypnea and may include features of respiratory compromise such as difficulty speaking due to respiratory effort, use of accessory respiratory muscles, and paradoxical chest wall/abdominal movements (asynchrony between chest and abdominal motion with respiration). Tachycardia is also frequently present.

If present, decreased mental status could reflect hypercapnia or hypoxemia and asterixis could indicate hypercapnia.

Attention should also be paid to other physical findings, such as fever, hypotension, bibasilar fine crackles and peripheral edema, which might suggest a comorbidity or alternate diagnosis.

EVALUATION AND DIAGNOSIS

The goals of the evaluation of a suspected exacerbation of COPD are to confirm the diagnosis, identify the cause (when possible), assess the severity of respiratory impairment and contribution from comorbidities, and exclude alternate diagnostic possibilities. A rapid overview for the evaluation and management of severe exacerbations of COPD is provided in the table (table 1).

Initial evaluation — The choice of specific tests is guided by the severity of the exacerbation and the particular associated clinical findings. (See 'Clinical manifestations' above.)

For patients with a mild exacerbation (absence of resting dyspnea or respiratory distress, preserved ability to perform activities of daily living), who do not require emergency department treatment, the evaluation may be limited to clinical assessment and possibly pulse oxygen saturation.

For patients who require emergency department care, the evaluation should generally include the following (table 1):

- Assessment of pulse oxygen saturation
- A chest radiograph to exclude pneumonia, pneumothorax, pulmonary edema, pleural effusion, followed by a chest CT angiogram to exclude pulmonary embolism in those whose chest radiograph does not reveal an acute process
- Laboratory studies (eg, complete blood count and differential, serum electrolytes and glucose)
- Arterial blood gas (ABG) analysis is obtained if acute or acute-on-chronic respiratory acidosis is suspected or if ventilatory support is anticipated. Concern about acute-on-chronic hypercapnia might be prompted by a history of prior elevation in arterial tension of carbon dioxide ($PaCO_2$), an elevated serum bicarbonate (perhaps reflecting compensation for chronic hypercapnia), or the presence of severe airflow obstruction (eg, forced expiratory volume in one second [FEV_1] <50 percent of predicted)

We do not use procalcitonin or C-reactive protein to determine the need for antibiotics in COPD exacerbations, as study results do not clearly and consistently demonstrate that either assay adds value to clinical judgment alone. (See "Evaluation for infection in exacerbations of chronic obstructive pulmonary disease", section on 'Procalcitonin and C-reactive protein'.)

Additional testing — Additional tests are largely used to exclude processes in the differential diagnosis and are obtained depending on the degree of diagnostic uncertainty following clinical evaluation and initial testing.

- **Electrocardiogram and blood cardiac troponins** are obtained to evaluate tachycardia and/or potential myocardial ischemia. (See "Initial evaluation and management of suspected acute coronary syndrome (myocardial infarction, unstable angina) in the emergency department".)

- **Plasma brain natriuretic peptide (BNP)** or NT-proBNP can help to exclude heart failure, as indicated by features such as crackles on chest auscultation, peripheral edema, suggestive chest radiographic findings (eg, vascular congestion, pleural effusion). If the clinical picture is unclear, an echocardiogram should be obtained. (See "Approach to diagnosis and evaluation of acute decompensated heart failure in adults".)

- **Chest CT pulmonary angiogram** can help exclude pulmonary embolism as a trigger or alternative diagnosis for respiratory symptoms. The frequency of pulmonary embolism in patients with COPD and acute respiratory symptoms in the hospital setting appears to be between 15 to 25 percent [43,48]. In one multicenter study of nearly 1600 patients hospitalized for COPD exacerbation who were assessed with CT pulmonary angiogram, the rates of pulmonary embolism based on low, moderate, or high probability Wells criteria scores were 7, 38, and 74 percent, respectively [43]. Purulent sputum production decreased the odds of venous thromboembolism by approximately 60 percent. Given this prevalence rate, we suggest obtaining imaging for pulmonary embolism (typically CT pulmonary angiogram) in patients with severe symptoms who do not have evidence of other triggers (eg, infection or heart failure). (See 'Differential diagnosis' below and "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism".)

- **Sputum Gram stain and culture** are not obtained for most exacerbations of COPD. However, sputum Gram stain and culture can be useful in patients at risk for a poor outcome or increased risk of infection with *Pseudomonas* (table 3 and table 4). Sputum culture may be helpful in patients who are strongly suspected of having a bacterial infection but fail to respond to initial antibiotic therapy. (See "Evaluation for infection in exacerbations of chronic obstructive pulmonary disease", section on 'When to obtain sputum studies'.)

- **Influenza testing** is appropriate during influenza season or in patients with features of influenza (eg, acute onset of fever, myalgias, coryza during an influenza outbreak). Rapid antigen testing and direct or indirect immunofluorescence antibody staining tests are useful screening tests for influenza infection but have limited sensitivity; polymerase chain reaction (PCR)-based testing is more sensitive and specific. (See "Seasonal influenza in adults: Clinical manifestations and diagnosis".)

- **COVID-19** – Test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the coronavirus disease 2019 (COVID-19) pandemic. (See "COVID-19: Diagnosis".)

- **Respiratory virus panel in selected patients** – The majority of COPD exacerbations are caused by viral infections, predominantly adenovirus. While not necessary in most patients, PCR diagnostic panels can detect multiple respiratory viruses simultaneously (eg, influenza, adenovirus, parainfluenza virus, respiratory syncytial virus, human metapneumovirus, coronavirus, and rhinovirus). These studies are more frequently

obtained in patients with community-acquired pneumonia, and the exact indications for their use in COPD exacerbations are not clear.

Severity of exacerbation — The classification of exacerbation severity proposed by an international commission and adopted by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is based on symptoms, vital signs, and arterial blood gas (ABG) and c-reactive protein values (if obtained) (figure 1) [1,23]:

- Mild – Dyspnea <5 on a visual analog (1-10) scale (VAS); respiratory rate <24 breaths per minute; heart rate <95 beats per minute; resting SaO2 ≥92 percent breathing ambient air or the patient's usual oxygen prescription **and** change in saturation ≤3 percent from baseline (if known); CRP<10 mg/L (if obtained). Treatment with short-acting bronchodilators is often sufficient for mild exacerbations.

- Moderate – Three out of five of the following: Dyspnea ≥5 on VAS; respiratory rate ≥24 breaths per minute, heart rate ≥95 beats per minute; resting SaO2 <92 percent breathing ambient air or the patient's usual oxygen prescription **and/or** change in saturation >3 percent from baseline (if known); CRP ≥10 mg/L (if obtained). Treatment of moderate exacerbations generally includes short-acting bronchodilators plus antibiotics and/or oral glucocorticoids.

- Severe – Meets moderate criteria combined with hypercapnia and acidosis on ABG (PaCO2 >45 mmHg **and** pH <7.35). Treatment of severe exacerbations includes short-acting bronchodilators, antibiotics, and oral or intravenous glucocorticoids. Severe exacerbations may be associated with respiratory failure and require noninvasive or invasive ventilation.

DIFFERENTIAL DIAGNOSIS

Patients with COPD who present to the hospital with acute worsening of dyspnea should be evaluated for potential alternative diagnoses, such as heart failure, cardiac arrhythmia, pneumonia, pulmonary embolism, and pneumothorax [1,50,51]. A chest radiograph will differentiate among several of these possibilities (eg, heart failure, pneumonia, pneumothorax); a clear chest radiograph may be a clue to pulmonary embolism, especially when dyspnea and hypoxemia are more prominent than cough or sputum production.

The importance of considering these alternate diagnoses was illustrated in an autopsy study of 43 patients with COPD who died within 24 hours of admission for a COPD exacerbation [50]. The primary causes of death were heart failure, pneumonia, pulmonary thromboembolism, and COPD in 37, 28, 21, and 14 percent, respectively.

- **Heart failure** – Acute decompensated heart failure (ADHF) is characterized by the development of acute dyspnea associated with elevated intracardiac filling pressures with or without pulmonary edema. HF may be new or an exacerbation of chronic disease. The diagnosis of ADHF is a clinical diagnosis based upon the presence of a constellation of symptoms and signs of HF. While test results (eg, natriuretic peptide level, chest radiograph, echocardiogram) are often supportive, the diagnosis cannot be based on a single test. (See "Approach to diagnosis and evaluation of acute decompensated heart failure in adults".)

- **Cardiac arrhythmias** – Cardiac arrhythmias, such as atrial fibrillation, are frequent in patients with COPD, and may be a trigger or consequence of COPD exacerbation [1]. A bedside electrocardiogram can be diagnostic. (See "Atrial fibrillation: Overview and management of new-onset atrial fibrillation".)

- **Pneumonia** – Pneumonia can present with acute shortness of breath, hypoxemia, and an inconclusive pulmonary examination. Chest radiograph findings may differ, but some cases of bibasilar pneumonia may be similar to HF, although evidence of upper zone redistribution is not present with pneumonia. Fever and leukocytosis may suggest an infectious process. (See "Clinical evaluation and diagnostic testing for community-acquired pneumonia in adults".)

- **Pneumothorax** – COPD is a risk factor for pneumothorax. Worsening dyspnea can be due to either a COPD exacerbation or pneumothorax, but acute pleuritic chest pain would be more suggestive of pneumothorax while increased volume of sputum and sputum purulence would suggest a COPD exacerbation. A pneumothorax is usually apparent on conventional chest radiograph or thoracic ultrasound, although bullous emphysema can mimic a pneumothorax and necessitate a chest computed tomography (CT) scan for differentiation. (See "Clinical presentation and diagnosis of pneumothorax".)

- **Pulmonary embolism** – The sudden onset of symptoms such as dyspnea, pleuritic chest pain, tachypnea, and cough may be caused by a pulmonary embolism. The suspicion for pulmonary embolism rises in the absence of purulent sputum production, history of an upper respiratory infection, or pneumothorax [42-48,52,53]. (See 'Triggers' above and 'Additional testing' above.)

  Testing may include a blood D-dimer test, lower extremity compression ultrasonography with Doppler, and CT pulmonary angiogram. (See "Clinical presentation, evaluation, and diagnosis of the nonpregnant adult with suspected acute pulmonary embolism".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic obstructive pulmonary disease".)

SUMMARY AND RECOMMENDATIONS

- **Definition** – A COPD exacerbation is an event characterized by dyspnea and/or cough and sputum production that worsens over ≤14 days and is often associated with increased local and systemic inflammation arising from airway infection, pollution, or other insult to the airways. (See "COPD exacerbations: Management", section on 'Introduction'.)

- **Risk factors** – Risk factors for exacerbations of COPD include advanced age, productive cough, duration of COPD, history of antibiotic therapy, COPD-related hospitalization within the previous year, chronic mucous hypersecretion, blood eosinophil count >0.34 x 10^9 cells/L (340 cells/microL), and comorbid disease. The single best predictor of exacerbations is a history of prior exacerbations. (See 'Risk factors and triggers' above and "COPD exacerbations: Prognosis, discharge planning, and prevention", section on 'Prognosis after an exacerbation'.)

- **Triggers** – Respiratory infections are estimated to trigger approximately 70 percent of COPD exacerbations. Viral and bacterial infections are most common; atypical bacterial infection is an uncommon trigger. Other potential triggers include myocardial ischemia, heart failure, aspiration, and pulmonary embolism. (See 'Triggers' above.)

- **Clinical manifestations**

  - **Symptoms** – The three cardinal symptoms of COPD exacerbation are dyspnea, cough, and/or sputum production; they can occur alone or in combination. Exacerbations typically develop over several hours to days. Symptoms such as fever, chills, night sweats, chest pain, or peripheral edema suggest an alternate or comorbid diagnosis. (See 'Clinical manifestations' above.)

  - **Physical exam findings** – Physical findings associated with an exacerbation of COPD often include wheezing and tachypnea and may include features of respiratory compromise. Patients should be examined for physical findings, such as fever,

hypotension, bibasilar fine crackles and peripheral edema, which might suggest a comorbidity or alternate diagnosis. (See 'Physical examination' above.)

- **Evaluation** – For patients who require emergency department care, the evaluation should generally include a pulse oxygen saturation, chest radiograph, complete blood count and differential, and serum electrolytes and glucose (table 1). Arterial blood gases (ABGs) are obtained when acute or acute-on-chronic hypercapnia is suspected due to prior elevation in arterial tension of carbon dioxide ($PaCO_2$), an elevated serum bicarbonate, or the presence of severe airflow obstruction (eg, FEV_1 <50 percent predicted). (See 'Initial evaluation' above.)

- **Differential diagnosis** – The most common processes in the differential diagnosis of a COPD exacerbation are heart failure, cardiac arrhythmias, pulmonary embolism, pneumonia, and pneumothorax. (See 'Differential diagnosis' above.)

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2024 Report. www.goldcopd.org www.goldcopd.org (Accessed on November 16, 2023).
2. Celli BR, Fabbri LM, Aaron SD, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. Am J Respir Crit Care Med 2021; 204:1251.
3. Seemungal TA, Donaldson GC, Paul EA, et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 157:1418.
4. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural History of Chronic Obstructive Pulmonary Disease Exacerbations in a General Practice-based Population with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2018; 198:464.
5. Lindenauer PK, Dharmarajan K, Qin L, et al. Risk Trajectories of Readmission and Death in the First Year after Hospitalization for Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2018; 197:1009.
6. Landis SH, Muellerova H, Mannino DM, et al. Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013. Int J Chron Obstruct Pulmon Dis 2014; 9:597.

7. Miravitlles M, Anzueto A, Legnani D, et al. Patient's perception of exacerbations of COPD--the PERCEIVE study. Respir Med 2007; 101:453.
8. Miravitlles M, Guerrero T, Mayordomo C, et al. Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study Group. Respiration 2000; 67:495.
9. Rascon-Aguilar IE, Pamer M, Wludyka P, et al. Role of gastroesophageal reflux symptoms in exacerbations of COPD. Chest 2006; 130:1096.
10. Niewoehner DE, Lokhnygina Y, Rice K, et al. Risk indexes for exacerbations and hospitalizations due to COPD. Chest 2007; 131:20.
11. Burgel PR, Nesme-Meyer P, Chanez P, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest 2009; 135:975.
12. Vedel-Krogh S, Nielsen SF, Lange P, et al. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med 2016; 193:965.
13. Oshagbemi OA, Keene SJ, Driessen JHM, et al. Trends in moderate and severe exacerbations among COPD patients in the UK from 2005 to 2013. Respir Med 2018; 144:1.
14. Rahman AA, Dell'Aniello S, Moodie EEM, et al. Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease : A Population-Based Cohort Study. Ann Intern Med 2024.
15. Rong Y, Bentley JP, McGwin G, et al. Association Between Transient Opioid Use and Short-Term Respiratory Exacerbation Among Adults With Chronic Obstructive Pulmonary Disease: A Case-Crossover Study. Am J Epidemiol 2019; 188:1970.
16. Vozoris NT, Fischer HD, Wang X, et al. Benzodiazepine use among older adults with chronic obstructive pulmonary disease: a population-based cohort study. Drugs Aging 2013; 30:183.
17. Vozoris NT, Fischer HD, Wang X, et al. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2014; 44:332.
18. Vozoris NT, Wang X, Fischer HD, et al. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J 2016; 48:683.
19. Castaneda JM, Hee Wai T, Spece LJ, et al. Risks of Zolpidem among Patients with Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc 2024; 21:68.
20. Stolz D, Kostikas K, Loefroth E, et al. Differences in COPD Exacerbation Risk Between Women and Men: Analysis From the UK Clinical Practice Research Datalink Data. Chest 2019; 156:674.

21. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010; 363:1128.
22. Soriano JB, Lamprecht B, Ramírez AS, et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. Lancet Respir Med 2015; 3:443.
23. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350:1005.
24. Terada K, Muro S, Sato S, et al. Impact of gastro-oesophageal reflux disease symptoms on COPD exacerbation. Thorax 2008; 63:951.
25. Kim J, Lee JH, Kim Y, et al. Association between chronic obstructive pulmonary disease and gastroesophageal reflux disease: a national cross-sectional cohort study. BMC Pulm Med 2013; 13:51.
26. Baumeler L, Papakonstantinou E, Milenkovic B, et al. Therapy with proton-pump inhibitors for gastroesophageal reflux disease does not reduce the risk for severe exacerbations in COPD. Respirology 2016; 21:883.
27. Bhatt SP, Agusti A, Bafadhel M, et al. Phenotypes, Etiotypes, and Endotypes of Exacerbations of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2023; 208:1026.
28. López-Sánchez M, Muñoz-Esquerre M, Huertas D, et al. High Prevalence of Left Ventricle Diastolic Dysfunction in Severe COPD Associated with A Low Exercise Capacity: A Cross-Sectional Study. PLoS One 2013; 8:e68034.
29. Farouk H, Albasmi M, El Chilali K, et al. Left ventricular diastolic dysfunction in patients with chronic obstructive pulmonary disease: Impact of methods of assessment. Echocardiography 2017; 34:359.
30. Bhatt SP, Dransfield MT. Chronic obstructive pulmonary disease and cardiovascular disease. Transl Res 2013; 162:237.
31. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med 2012; 367:913.
32. Sapey E, Bafadhel M, Bolton CE, et al. Building toolkits for COPD exacerbations: lessons from the past and present. Thorax 2019; 74:898.
33. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008; 359:2355.

34. Mohan A, Chandra S, Agarwal D, et al. Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. Respirology 2010; 15:536.
35. Barnes PJ. Chronic obstructive pulmonary disease. N Engl J Med 2000; 343:269.
36. Sapey E, Stockley RA. COPD exacerbations . 2: aetiology. Thorax 2006; 61:250.
37. Gan WQ, FitzGerald JM, Carlsten C, et al. Associations of ambient air pollution with chronic obstructive pulmonary disease hospitalization and mortality. Am J Respir Crit Care Med 2013; 187:721.
38. de Miguel-Díez J, Hernández-Vázquez J, López-de-Andrés A, et al. Analysis of environmental risk factors for chronic obstructive pulmonary disease exacerbation: A case-crossover study (2004-2013). PLoS One 2019; 14:e0217143.
39. Ross BA, Doiron D, Benedetti A, et al. Short-term air pollution exposure and exacerbation events in mild to moderate COPD: a case-crossover study within the CanCOLD cohort. Thorax 2023; 78:974.
40. Li MH, Fan LC, Mao B, et al. Short-term Exposure to Ambient Fine Particulate Matter Increases Hospitalizations and Mortality in COPD: A Systematic Review and Meta-analysis. Chest 2016; 149:447.
41. Hansel NN, Putcha N, Woo H, et al. Randomized Clinical Trial of Air Cleaners to Improve Indoor Air Quality and Chronic Obstructive Pulmonary Disease Health: Results of the CLEAN AIR Study. Am J Respir Crit Care Med 2022; 205:421.
42. Tillie-Leblond I, Marquette CH, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. Ann Intern Med 2006; 144:390.
43. Liu X, Jiao X, Gong X, et al. Prevalence, Risk Factor and Clinical Characteristics of Venous Thrombus Embolism in Patients with Acute Exacerbation of COPD: A Prospective Multicenter Study. Int J Chron Obstruct Pulmon Dis 2023; 18:907.
44. Pourmand A, Robinson H, Mazer-Amirshahi M, Pines JM. Pulmonary Embolism Among Patients With Acute Exacerbation Of Chronic Obstructive Pulmonary Disease: Implications For Emergency Medicine. J Emerg Med 2018; 55:339.
45. Hassen MF, Tilouche N, Jaoued O, Elatrous S. Incidence and Impact of Pulmonary Embolism During Severe COPD Exacerbation. Respir Care 2019; 64:1531.
46. Couturaud F, Bertoletti L, Pastre J, et al. Prevalence of Pulmonary Embolism Among Patients With COPD Hospitalized With Acutely Worsening Respiratory Symptoms. JAMA 2021; 325:59.

47. Jiménez D, Agustí A, Tabernero E, et al. Effect of a Pulmonary Embolism Diagnostic Strategy on Clinical Outcomes in Patients Hospitalized for COPD Exacerbation: A Randomized Clinical Trial. JAMA 2021; 326:1277.
48. Sato R, Hasegawa D, Nishida K, et al. Prevalence of pulmonary embolism in patients with acute exacerbations of COPD: A systematic review and meta-analysis. Am J Emerg Med 2021; 50:606.
49. Anthonisen NR, Manfreda J, Warren CP, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987; 106:196.
50. Zvezdin B, Milutinov S, Kojicic M, et al. A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. Chest 2009; 136:376.
51. Myint PK, Lowe D, Stone RA, et al. U.K. National COPD Resources and Outcomes Project 2008: patients with chronic obstructive pulmonary disease exacerbations who present with radiological pneumonia have worse outcome compared to those with non-pneumonic chronic obstructive pulmonary disease exacerbations. Respiration 2011; 82:320.
52. Rizkallah J, Man SFP, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2009; 135:786.
53. Aleva FE, Voets LWLM, Simons SO, et al. Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A Systematic Review and Meta-analysis. Chest 2017; 151:544.

Topic 122144 Version 21.0

GRAPHICS

Severe COPD exacerbation: Rapid overview of emergency management

Clinical features
Features of COPD exacerbation: Diffuse wheezing, distant breath sounds, barrel-shaped chest, tachypnea, tachycardia, smoking >20 pack years.
Features of severe respiratory insufficiency: Use of accessory muscles; brief, fragmented speech; inability to lie supine; profound diaphoresis; agitation; asynchrony between chest and abdominal motion with respiration; failure to improve with initial emergency treatment.
Features of impending respiratory arrest: Inability to maintain respiratory effort, cyanosis, hemodynamic instability, and depressed mental status
Features of cor pulmonale: Jugular venous distension, prominent left parasternal heave, peripheral edema.
COPD exacerbations are most often precipitated by infection (viral or bacterial).
Severe respiratory distress in a patient with known or presumed COPD can be due to an exacerbation o COPD or a comorbid process, such as acute coronary syndrome, decompensated heart failure, pulmonary embolism, pneumonia, pneumothorax, sepsis.
Management
Assess patient's airway, breathing, and circulation; secure as necessary.
Provide supplemental oxygen to target a pulse oxygen saturation of 88 to 92% or PaO_2 of 60 to 70 mmHg (7.98 to 9.31 kPa); Venturi mask can be useful for titrating FiO_2; high FiO_2 usually not needed an can contribute to hypercapnia (high FiO_2 requirement should prompt consideration of alternative diagnosis [eg, PE]).
Determine patient preferences regarding intubation based on direct questioning or advance directive whenever possible.
Provide combination of aggressive bronchodilator therapy and ventilatory support (NIV or invasive ventilation).
Noninvasive ventilation (NIV): Appropriate for the majority of patients with severe exacerbations of COPD unless immediate intubation is needed or NIV is otherwise contraindicated
Contraindications to NIV include: Severely impaired consciousness, inability to clear secretions or protect airway, high aspiration risk.
Initial settings for bilevel NIV: 8 cm H_2O inspiratory pressure (may increase up to 15 cm H_2O if needed t aid ventilation); 3 cm H_2O expiratory pressure.
Administer bronchodilators via nebulizer or MDI: Nebulizer usually requires interruption of NIV; MDIs can be delivered in line using adaptor (refer to dosing below).

Obtain ABG after two hours of NIV and compare with baseline: Worsening or unimproved gas exchange and pH <7.25 are indications for invasive ventilation.
Tracheal intubation and mechanical ventilation: Indicated for patients with acute respiratory failure hemodynamic instability (eg, heart rate <50/minute, uncontrolled arrhythmia) and those in whom NIV is contraindicated or who fail to improve with NIV and aggressive pharmacotherapy
Rapid sequence induction (eg, etomidate, ketamine, or propofol).
Intubate with #8 endotracheal tube (8 mm internal diameter) or larger, if possible.
Initial ventilator settings aim to maintain adequate oxygenation and ventilation while minimizing elevated airway pressures: SIMV, tidal volume 6 to 8 mL/kg, respiratory rate 10 to 12/minute, inspiratory flow rate 60 to 80 L/min (increase if needed to enable longer expiratory phase), PEEP 5 cm H_2O. May need to tolerate elevated $PaCO_2$ to avoid barotrauma (ie, permissive hypercapnia). In patients with chronic hypercapnia, aim for $PaCO_2$ close to baseline.
Administer inhaled bronchodilator therapy: Usually via MDI with in-line adaptor (refer to dosing below).
Diagnostic testing
Assess oxygen saturation with continuous pulse oximetry.
Obtain ABG in all patients with severe COPD exacerbation.
$ETCO_2$ monitoring (capnography) has only moderate correlation with arterial $PaCO_2$ in COPD exacerbations.
Do not assess peak expiratory flow or spirometry in acute severe COPD exacerbations as results are not accurate.
Obtain portable chest radiograph: Look for signs of pneumonia, acute heart failure, pneumothorax.
When evidence of acute infection (eg, purulent phlegm, pneumonia) is absent and chest radiograph is unrevealing, obtain CT pulmonary angiogram for possible pulmonary embolism.
Obtain complete blood count, electrolytes (Na+, K+, Cl–, HCO3–), BUN, and creatinine; also obtain cardiac troponin, BNP, or NT-proBNP, if diagnosis is uncertain.
Test for influenza infection during influenza season.*
Obtain ECG: Look for arrhythmia, ischemia, cor pulmonale.
Pharmacotherapy
Inhaled beta agonist: Albuterol 2.5 mg diluted to 3 mL via nebulizer or 2 to 4 inhalations from MDI every hour for 2 or 3 doses; up to 8 inhalations may be used for intubated patients, if needed.
Short-acting muscarinic antagonist (anticholinergic agent): Ipratropium 500 micrograms (can be combined with albuterol) in 3 mL via nebulizer or 2 to 4 inhalations from MDI every hour for 2 to 3 doses.
Intravenous glucocorticoid (eg, methylprednisolone 60 mg to 125 mg IV, repeat every 6 to 12 hours).
Antibiotic therapy*: Appropriate for majority of severe COPD exacerbations; select antibiotic based on likelihood of particular pathogens (eg, *Pseudomonas* risk factors¶, prior sputum cultures, local patterns

of resistance).
▪ No *Pseudomonas* risk factor(s)¶: Ceftriaxone 1 to 2 grams IV, **or** cefotaxime 1 to 2 grams IV, **or** levofloxacin 500 mg IV or orally, **or** moxifloxacin 400 mg IV or orally
▪ *Pseudomonas* risk factor(s)¶: Piperacillin-tazobactam 4.5 grams IV, **or** cefepime 2 grams IV, **or** ceftazidime 2 grams IV
Antiviral therapy (influenza suspected)*: Oseltamivir 75 mg orally every 12 hours **or** peramivir 600 mg IV once (for patients unable to take oral medication).
Monitoring
Perform continual monitoring of oxygen saturation, blood pressure, heart rate, respiratory rate.
Close monitoring of respiratory status.
Continuous ECG monitoring.
Monitor blood glucose.
Disposition
Criteria for ICU admission include:
▪ Patients with high-risk comorbidities (pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal failure, liver failure)
▪ Continued need for NIV or invasive ventilation
▪ Hemodynamic instability
▪ Need for frequent nebulizer treatments or monitoring

COPD: chronic obstructive pulmonary disease; PaO_2: arterial tension of oxygen; FiO_2: fraction of inspired oxygen; PE: pulmonary embolism; NIV: noninvasive ventilation; MDI: metered dose inhaler; ABG: arterial blood gas; SIMV: synchronized intermittent mechanical ventilation; PEEP: positive end-expiratory pressure; $PaCO_2$: arterial tension of carbon dioxide; $ETCO_2$: end-tidal carbon dioxide; BUN: blood urea nitrogen; BNP: brain natriuretic peptide; NT-ProBNP: N-terminal pro-BNP; ECG: electrocardiogram; IV: intravenous; ICU: intensive care unit.

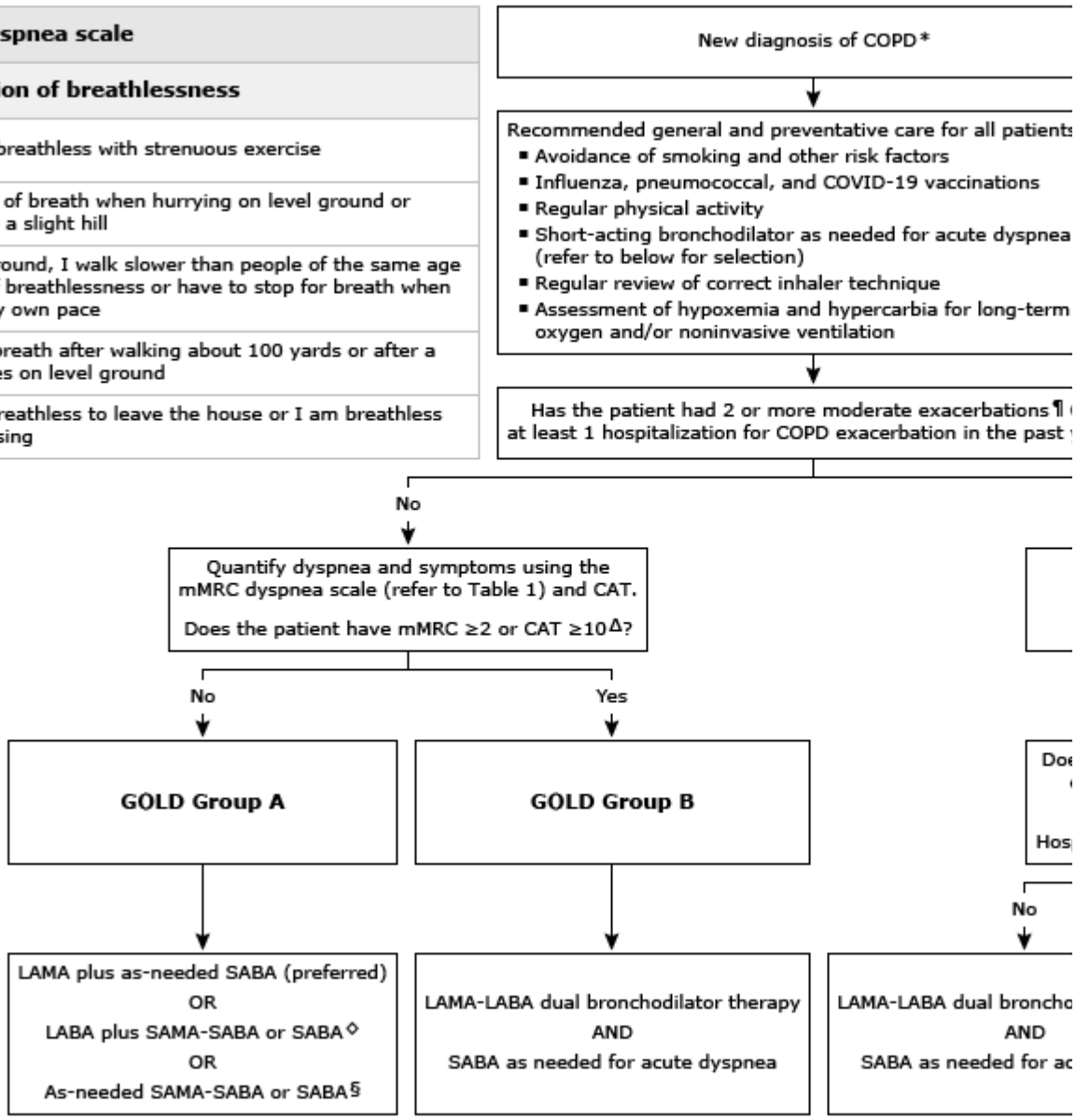
* When influenza is suspected, therapy should not be delayed while awaiting results of testing. Doses shown are for patients with normal renal function. Some agents require dose adjustment for renal impairment; refer to separate UpToDate algorithms of antibiotic treatment of exacerbations of COPD.

¶ *Pseudomonas* infection risk factors: Broad spectrum antibiotic use in the past 3 months; chronic colonization or previous isolation of Pseudomonas aeruginosa from sputum (particularly in past 12 months); very severe underlying COPD (FE_V1 <30% predicted); chronic systemic glucocorticoid use.

New diagnosis of COPD

Table 1: mMRC dyspnea scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing



COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CAT: COPD Assessment Test; SABA: short-acting beta-agonist; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist (anticholinergic); LABA: long-acting beta-agonist; mMRC: Modified Medical Research Council; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

* COPD is diagnosed based on the presence of chronic respiratory symptoms (dyspnea, cough, sputum production) accompanied by airflow limitation. All patients with COPD defined by GOLD have airflow limitation based on a reduced FEV_1/FVC ratio <0.70. The severity of airflow limitation is determined by the reduction in FEV_1.

¶ An exacerbation of COPD is characterized by increased dyspnea and/or cough and sputum that worsens in less than 14 days, may be accompanied by tachypnea or tachycardia, and is often caused by infection, environmental irritation, or other insult to the airways. "Moderate exacerbations" are typically defined as those which require treatment with systemic glucocorticoids. More objective severity

classifications have been proposed but are difficult to establish via patient history. Please refer to UpToDate content on "COPD exacerbations: Clinical manifestations and evaluation" for additional information.

Δ CAT: http://www.catestonline.org (Accessed on January 12, 2023).

◇ For those prescribed a LABA alone, SAMA-SABA combination therapy is likely to be most potent but will have some of the same side effects as LAMA. For those prescribed a LAMA, SAMA should generally not be used concomitantly, so SABA alone is preferred.

§ Occasional patients with only minimal intermittent symptoms are appropriate for only as-needed rescue therapy rather than treatment with long-acting bronchodilators.

Graphic 54300 Version 13.0

Relative frequency of bacterial pathogens isolated from 14 antibiotic comparison trials in exacerbations of chronic obstructive pulmonary disease*

Pathogen	Percentage of bacterial isolates (range)
Haemophilus influenzae	13 to 50
Moraxella catarrhalis	9 to 21
Streptococcus pneumoniae	7 to 26
Pseudomonas aeruginosa	1 to 13

* Enterobacteriaceae have been isolated from the respiratory tract of 3 to 19 percent of patients with chronic obstructive pulmonary disease (COPD) exacerbations and *Staphylococcus aureus* has been isolated from the respiratory tract of 1 to 20 percent of patients with COPD exacerbations, but their pathogenic significance in this setting has not been defined. *Haemophilus parainfluenzae* has been isolated from the respiratory tract of 2 to 32 percent of patients with COPD exacerbations, but these organisms are unlikely to cause COPD exacerbations.

Graphic 70203 Version 9.0

Risk factors for poor outcomes in patients with acute COPD exacerbations

▪ Comorbid conditions (especially heart failure or ischemic heart disease)
▪ Severe underlying COPD (eg, FEV_1 <50%)
▪ Frequent exacerbations of COPD (ie, ≥2 exacerbations per year)
▪ Hospitalization for an exacerbation within the past 3 months
▪ Receipt of continuous supplemental oxygen
▪ Age ≥65 years*

Patients with greater underlying COPD severity are at higher risk for poor outcomes if initial antibiotic therapy is inadequate. We thus use a broader empiric regimen for such patients.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second.

* Older age (eg, age ≥65 years) is also associated with poorer outcomes and/or risk of infection with drug-resistant pathogens. While not a strict indication for broadening antibiotic therapy, we consider older age as additive to the risk factors listed above.

References:

1. *Balter MS, La Forge J, Low DE, et al. Canadian guidelines for the management of acute exacerbations of chronic bronchitis. Can Respir J 2003; 10 Suppl B:3B.*
2. *Miravitlles M, Murio C, Guerrero T. Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group. Eur Respir J 2001; 17:928.*
3. *Wilson R, Jones P, Schaberg T, et al. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. Thorax 2006; 61:337.*
4. *Garcia-Vidal C, Almagro P, Romaní V, et al. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J 2009; 34:1072.*
5. *Parameswaran GI, Sethi S. Pseudomonas infection in chronic obstructive pulmonary disease. Future Microbiol 2012; 7:1129.*

Graphic 126161 Version 1.0

Risk factors for infection with *Pseudomonas aeruginosa* in patients with acute COPD exacerbations

▪ Chronic colonization or previous isolation of *Pseudomonas aeruginosa* from sputum (particularly in the past 12 months)
▪ Very severe COPD (FEV_1 <30% predicted)
▪ Bronchiectasis on chest imaging
▪ Broad-spectrum antibiotic use within the past 3 months
▪ Chronic systemic glucocorticoid use

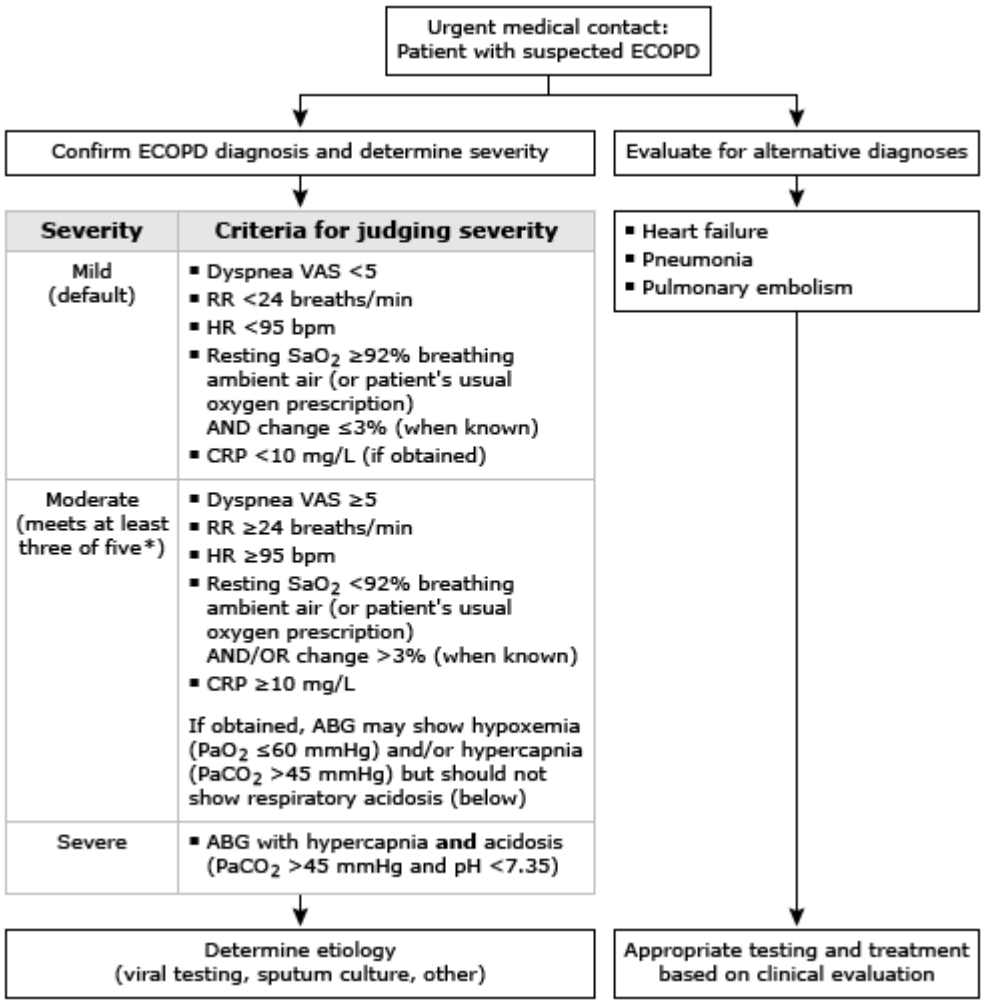
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second.

References:

1. *Garcia-Vidal C, Almagro P, Romaní V, et al. Pseudomonas aeruginosa in patients hospitalised for COPD exacerbation: a prospective study. Eur Respir J 2009; 34:1072.*
2. *Parameswaran GI, Sethi S. Pseudomonas infection in chronic obstructive pulmonary disease. Future Microbiol 2012; 7:1129.*
3. *Gallego M, Pomares X, Espasa M, et al. Pseudomonas aeruginosa isolates in severe chronic obstructive pulmonary disease: characterization and risk factors. BMC Pulm Med 2014; 14:103.*
4. *Boixeda R, Almagro P, Díez-Manglano J, et al. Bacterial flora in the sputum and comorbidity in patients with acute exacerbations of COPD. Int J Chron Obstruct Pulmon Dis 2015; 10:2581.*

Graphic 126162 Version 1.0

Initial assessment of suspected COPD exacerbation severity and etiology



Diagnostic flowchart for assessment of suspected COPD exacerbation severity and etiology.

ECOPD: exacerbation of chronic obstructive pulmonary disease; ABG: arterial blood gas; CRP: C-reactive protein; HR: heart rate; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; pH: arterial acid-base status; RR: respiratory rate; SaO_2: peripheral arterial oxygen saturation, as determined by pulse oximetry; VAS: visual analog scale.

* Dyspnea (as determined by VAS), RR, HR, oxygen saturation (absolute and/or change), and CRP.

Graphic 140565 Version 1.0