COPD exacerbations: Management

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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 management of patients with exacerbations of COPD is discussed here. A table to assist with emergency management of severe acute exacerbations of COPD is provided (table 1). The diagnosis and treatment of infection in exacerbations and the management of stable COPD are discussed separately.

- (See "COPD exacerbations: Clinical manifestations and evaluation".)
- (See "COPD exacerbations: Prognosis, discharge planning, and prevention".)
- (See "Evaluation for infection in exacerbations of chronic obstructive pulmonary disease".)

- (See "Management of infection in exacerbations of chronic obstructive pulmonary disease".)
- (See "Stable COPD: Overview of management".)

TRIAGE TO HOME OR HOSPITAL

An important step in the initial evaluation is to determine whether the patient needs hospitalization or can be safely managed at home (algorithm 1) [1,3]. More than 80 percent of exacerbations of COPD can be managed on an outpatient basis, sometimes after initial treatment in the office or emergency department. If the exacerbation appears life-threatening or if there are indications for ventilatory support (eg, hypoxemic or hypercapnic respiratory failure), the patient should be admitted to the intensive care unit as quickly as possible. (See 'Ventilatory support' below.)

Other criteria that might lead to a decision to hospitalize the patient have been proposed in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines and international consensus statements include [1,2,4]:

- Inadequate response to outpatient or emergency department management
- Onset of new signs (eg, cyanosis, altered mental status, peripheral edema)
- Marked increase in intensity of symptoms over baseline (eg, new onset resting dyspnea) accompanied by increased oxygen requirement
- Signs of respiratory distress (use of accessory respiratory muscles or paradoxical chest wall movements, or both)
- Serious comorbidities including pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal failure, or liver failure
- Hemodynamic instability
- Insufficient home support

Prior guidelines have also included severe airflow limitation, a history of frequent or severe exacerbations, and frailty as factors associated with increased risk for severe exacerbations. These factors may also be considered in triaging COPD patients for hospital admission.

Intensive home care, which generally includes nurse visits, home oxygen, and physical therapy, may be an alternative to hospitalizations in certain locations (eg, United Kingdom, Europe) for selected patients with an exacerbation of COPD [5-9]. A meta-analysis of seven trials noted that intensive home care resulted in equivalent clinical outcomes and substantial cost savings compared to hospitalization [10]. However, these trials excluded sicker patients with an

impaired level of consciousness, respiratory acidosis (arterial pH <7.35), acute electrocardiographic or chest radiographic changes, or coexisting medical morbidities. Although care at home is feasible in highly selected patients without these characteristics, implementation requires a dedicated support team to conduct ongoing clinical assessments and provide home care. In general, home management of the patient who satisfies criteria for hospitalization should be considered infrequently and only when optimal home care is available.

HOME OR OFFICE MANAGEMENT OF COPD EXACERBATIONS

Home management of COPD exacerbations generally includes intensification of bronchodilator therapy and initiation of a course of oral glucocorticoids; oral antibiotics are added based on individual characteristics.

Home/office short-acting bronchodilator treatments — We recommend that all patients with a COPD exacerbation receive inhaled short-acting bronchodilator therapy.

- **Beta-adrenergic agonists** – Inhaled short-acting beta- (adrenergic) agonists (SABA; eg, albuterol, levalbuterol) are the mainstay of therapy for an acute exacerbation of COPD because of their rapid onset of action and efficacy in producing bronchodilation [1,11,12]. Albuterol is sometimes combined with an additional short-acting bronchodilator (the short-acting muscarinic antagonist [SAMA] ipratropium) in a soft mist inhaler (SMI).

  Occasional patients with more severe COPD or difficulty with inhaler technique may take albuterol or levalbuterol by nebulization at home. The usual dose of albuterol for nebulization is 2.5 mg (diluted to a total of 3 mL with sterile normal saline, resulting in 2.5 mg/3 mL or 0.083 percent). For COPD exacerbations, this dose can be repeated every 20 to 60 minutes for two to three doses and then every two to four hours as needed based on the patient's response. Levalbuterol dosing for nebulization is 0.63 to 1.25 mg (diluted to 3 mL) and administered at the same intervals as noted for albuterol.

  Patients who already have a nebulizer at home frequently report that bronchodilator administration via nebulizer is helpful during COPD exacerbations. However, most studies have not supported a greater effect from nebulizer treatments over properly administered metered dose inhaler medication. Nebulized albuterol can be combined with ipratropium. (See 'Hospital-based bronchodilator therapies' below and "Delivery of inhaled medication in adults", section on 'Home use'.)

- **Muscarinic antagonists** – Ipratropium bromide, an inhaled SAMA (also known as a short-acting anticholinergic agent) is often used in combination with inhaled SABA [1]. It is generally not used as monotherapy due to the longer time to onset of action compared with SABAs.

  The usual dose of ipratropium for an acute exacerbation of COPD is two inhalations by metered dose inhaler (MDI) every four to six hours. The usual dose of a combination ipratropium and albuterol SMI is **one** inhalation by SMI (Respimat) every four to six hours. When administering by nebulizer, the dose of ipratropium is 0.5 mg/2.5 mL (0.02 percent; one unit-dose vial) every 6 to 8 hours. Alternatively, ipratropium 0.5 mg/2.5 mL can be combined with albuterol 2.5 mg/0.5 mL (total 3 mL).

  The evidence for adding a SAMA to SABA comes from a few studies in which combination therapy produced bronchodilation in excess of that achieved by either agent alone in patients with a COPD exacerbation or stable COPD [13,14]. However, this finding has not been universal, and other studies not found an additive effect in COPD exacerbations [15,16]. A longer duration of bronchodilation has been observed with the addition of ipratropium to albuterol in stable COPD [17].

  For patients who have a history of benign prostatic hypertrophy or prior urinary retention, the addition of ipratropium to a long-acting muscarinic antagonist (LAMA; eg, aclidinium, glycopyrrolate, tiotropium, umeclidinium) may increase the risk of acute urinary retention, although data are conflicting. (See "Role of muscarinic antagonist therapy in COPD", section on 'Acute urinary retention'.)

Continued use of long-acting bronchodilators during exacerbations — While continuation of ongoing therapy with long-acting beta agonists (LABAs) or LAMAs has not been specifically studied, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy advises their continuation [1].

Home oral glucocorticoid therapy — For outpatients with a COPD exacerbation characterized by breathlessness that interferes with daily activities, systemic glucocorticoid therapy appears to have a small but beneficial effect with a reduction in rate of relapse. Patients with elevated eosinophil counts at the time of exacerbation are most likely to benefit [18-20]. Our practice reflects current guidelines, which suggest using a dose that is the equivalent of prednisone 40 mg per day for 5 to 14 days [1,3,12]. Occasional patients may benefit from a higher dose or a longer course depending on the severity of the exacerbation and response to prior courses of glucocorticoids.

The benefit of oral glucocorticoids in the outpatient management of COPD exacerbations was examined in a randomized trial of 147 patients discharged from the emergency department after presenting with an acute exacerbation of COPD [21]. Patients received oral prednisone (40 mg) or placebo for 10 days. Patients who received prednisone were less likely to return to the emergency department or their clinician with increasing dyspnea within 30 days (27 versus 43 percent, p = 0.05) (figure 1). In addition to a lower rate of relapse (the primary end point of the study), prednisone therapy was associated with decreased dyspnea and a greater improvement in forced expiratory volume in one second (FEV_1; 34 versus 15 percent) on day 10.

The REDUCE trial showed that a five-day course of methylprednisolone (day one intravenously, orally thereafter) was noninferior to a 14-day course regarding the risk of recurrent exacerbation over six months of follow-up [22]. Although over 90 percent of the patients in the trial were initially admitted, these findings can likely be extrapolated to the less ill outpatient population. (See 'Glucocorticoids in moderate to severe exacerbations' below.)

In the STARR2 trial, patients presenting to a primary care clinic with COPD exacerbation were assigned to either an eosinophil-based triage strategy, where 14 days of systemic glucocorticoids (30 mg of oral prednisolone daily) were offered only to those with relative eosinophilia (≥2 percent) at the time of exacerbation, or to a 14-day course of glucocorticoids regardless of eosinophil status [18]. The two strategies were found to be noninferior in the trial; glucocorticoid treatment did not improve and may have worsened respiratory symptoms and treatment failure rates in those without eosinophil elevations. However, some adverse effects may have arisen from the relatively long glucocorticoid treatment course used in this trial, and the need for point-of-care blood testing may be a significant barrier to implementation in some primary care settings. Our authors feel that further study is necessary before widespread adoption of an eosinophil-directed treatment strategy.

Patients should be warned of potential adverse effects of systemic glucocorticoids that may require mitigation, particularly hyperglycemia (in patients with diabetes mellitus), fluid retention, and hypertension. (See "Major adverse effects of systemic glucocorticoids".)

Inhaled glucocorticoids as an alternative approach — A few trials have examined high-dose budesonide as an alternative to systemic glucocorticoids for COPD exacerbations, but have largely studied hospitalized patients who did not require intensive care unit (ICU) admission and have examined physiologic outcomes, such as FEV_1 improvement [23,24]. Further study is needed to establish efficacy before this strategy is broadly used.

In a systematic review and meta-analysis (9 studies, nearly 1000 patients), high-dose nebulized budesonide (4 to 8 mg/day) had a similar effect to oral glucocorticoids in patients hospitalized

for a COPD exacerbation for change in FEV_1 (weighted mean difference 0.05 L/sec [95% CI -0.01–0.12]) or arterial tension of carbon dioxide ($PaCO_2$), but was slightly inferior for oxygenation improvement [23].

A separate trial in 109 out-patients with a COPD exacerbation found that use of the high-dose combination inhaler, budesonide-formoterol (320 mcg-9 mcg) 1 inhalation four times daily, resulted in a similar change in FEV_1 compared with oral prednisolone 30 mg daily plus inhaled formoterol [25].

Antimicrobial therapy, in selected outpatients

- **Antibiotics** – To try to maximize the benefit of antibiotic therapy, clinical practice guidelines recommend antibiotic therapy only for those patients who are most likely to have bacterial infection or are most ill. The role of antibiotics in exacerbations of COPD, including antibiotic selection, is discussed in detail separately. (See "Management of infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations' and "Evaluation for infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations'.)

  In brief, the GOLD strategy recommends empiric antibiotics for patients with COPD exacerbations who have increased sputum purulence and either increased sputum volume or increased dyspnea, or for patients who require ventilatory assistance [1]. Patients without these risk factors should not receive up-front antibiotic therapy without radiographic or microbiologic evidence of pulmonary infection. The choice of empiric therapy varies based on both patient-specific factors and local resistance patterns (algorithm 2).

- **Antiviral agents** – For patients with a COPD exacerbation during influenza season, we screen for influenza infection, with a preference for molecular assays over rapid antigen tests. If influenza infection is suspected, we initiate empiric antiviral therapy without waiting for laboratory confirmation. (See "Management of infection in exacerbations of chronic obstructive pulmonary disease", section on 'Respiratory virus treatment' and "Seasonal influenza in adults: Clinical manifestations and diagnosis".)

  Severe acute respiratory syndrome coronavirus (SARS-CoV)-2, the cause of coronavirus disease-2019 (COVID-2019), can mimic or result in a COPD exacerbation. When an exacerbation of COPD occurs in the course of COVID-19, the usual guidelines for prompt initiation of systemic glucocorticoids for a COPD exacerbation should be followed, as delaying therapy can increase the risk of a life-threatening exacerbation. Patients with COPD are at increased risk for severe respiratory illness associated with COVID-19 and

therefore qualify for prioritized outpatient therapy. Diagnosis and treatment of COVID-19 are discussed separately. (See "COVID-19: Diagnosis" and 'Antiviral and antimicrobial agents' below and "COVID-19: Management of adults with acute illness in the outpatient setting".)

Adjunctive care — For patients being managed at home, supportive care often includes advice regarding cigarette smoking cessation and medication adherence. Some patients may need nutritional support and a review of goals of care. Patients who have a new requirement for supplemental oxygen are usually managed in the hospital, at least initially. (See 'Triage to home or hospital' above and "Overview of smoking cessation management in adults" and "Malnutrition in advanced lung disease" and "Pulmonary rehabilitation".)

EMERGENCY DEPARTMENT AND HOSPITAL MANAGEMENT

Similar to at-home management, the major components of emergency department or in-hospital management of exacerbations of COPD include reversing airflow limitation with inhaled short-acting bronchodilators and systemic glucocorticoids, treating infection, ensuring appropriate oxygenation, and averting intubation and mechanical ventilation [1,26]. An approach to emergency management of severe exacerbations of COPD is summarized in the table (table 1).

For patients who are admitted to the hospital, the severity of the exacerbation is classified based on clinical signs [1,2]:

- **No respiratory failure** – Respiratory rate ≤24 breaths per minute; heart rate (HR) <95 beats per minute; no use of accessory respiratory muscles; no change in mental status; pulse oxygen saturation (SpO_2) 88 to 92 percent with Venturi mask 24 to 35 percent inspired oxygen (or equivalent); no hypercapnia.

- **Acute nonlife-threatening respiratory failure** – Respiratory rate >24 breaths per minute; use of accessory muscles of respiration; no change in mental status; SpO_2 88 to 92 percent with Venturi mask 24 to 35 percent (or equivalent); arterial tension of carbon dioxide ($PaCO_2$) 50 to 60 mmHg or increased over baseline.

- **Acute life-threatening respiratory failure** – Respiratory rate >24 breaths per minute; use of accessory muscles of respiration; acute change in mental status; requiring fraction of inspired oxygen (FiO_2) ≥40 percent to maintain SpO_2 88 to 92 percent; $PaCO_2$ increased compared with baseline or >60 mmHg or associated with acidosis (pH ≤7.25).

Monitoring — In-hospital monitoring typically includes frequent assessment of respiratory status (eg, respiratory rate and effort, wheezing, pulse oxygen saturation), heart rate and rhythm, blood pressure, and also fluid status. Patients who require admission to the intensive care unit (ICU) should have continuous monitoring of vital signs and oxygenation. Arterial blood gas measurement is performed to assess for respiratory acidosis (eg, prior hypercapnia, severe exacerbation, or deterioration of patient's respiratory status during treatment), confirm the accuracy of pulse oxygen saturation, and to monitor known hypercapnia. (See "Simple and mixed acid-base disorders", section on 'Respiratory acid-base disorders'.)

Initial pharmacologic therapy

Hospital-based bronchodilator therapies — We recommend that all patients with an exacerbation of COPD receive prompt treatment with an inhaled short-acting beta- (adrenergic) agonist (SABAs; eg, albuterol, levalbuterol) because of their rapid onset of action and efficacy in producing bronchodilation in COPD [1,3]. We further suggest use of the combination of a short-acting muscarinic antagonist (SAMA; eg, ipratropium) **and** SABA for exacerbations that require emergency department or hospital-based treatment, based on the benefit of dual therapy in stable COPD [1,16,27].

- **SAMA-SABA combination therapy** – When combined with albuterol for nebulization, ipratropium 0.5 mg (500 mcg) is mixed with albuterol 2.5 mg in 3 mL and given every hour for two or three doses and then every two to four hours as needed. In patients with potential viral infections resulting in COPD exacerbation, particularly SARS-CoV-2, nebulized medications should ideally be avoided or limited to use in negative pressure rooms to decrease disease spread.

  Alternatively, a combination ipratropium-albuterol soft mist inhaler (SMI) can be used, one inhalation, approximately every 20 to 60 minutes for two to three doses and then every two to four hours as needed, guided by the response to therapy [28]. Ipratropium is also available in a metered dose inhaler (MDI) that can be used with a spacer, two to four inhalations every hour for two to three doses, and then every two to four hours as needed. (See "Role of muscarinic antagonist therapy in COPD".)

  Combination therapy with albuterol and ipratropium is clearly superior to albuterol alone in stable COPD, but studies in acute exacerbations are limited [14,16]. A systematic review identified a small number of trials that compared a combination of SAMA (ipratropium) plus SABA (albuterol, metaproterenol, fenoterol) with SABA alone and did not find an added benefit to the combination when assessed at 90 minutes [16]. Nevertheless, this

combination is often used to treat COPD exacerbations given extensive evidence of superior bronchodilation in longer term studies.

- **SABA therapy alone** – Typical doses of albuterol in this setting are 2.5 mg (diluted to a total of 3 mL with sterile normal saline) by nebulizer or one to two inhalations (most commonly two, occasionally four; 90 mcg per inhalation) by MDI with a spacer every 20 to 60 minutes for two to three doses and then every two to four hours as needed, guided by the response to therapy [1]. For patients requiring mechanical ventilation, up to eight inhalations may be given if needed. Levalbuterol is given at equipotent doses (ie, 1.25 mg in 3 mL sterile saline for nebulization and 45 mcg per inhalation via MDI).

  Despite evidence that MDI devices have equal efficacy during exacerbations of COPD, many clinicians prefer nebulized therapy on the presumption of more reliable delivery of drug to the airway [1]. We favor nebulized therapy because many patients with COPD have difficulty using proper MDI technique in the setting of an exacerbation. Air-driven nebulizers are preferred over oxygen delivered nebulizers to minimize the risk of increasing $PaCO_2$ [29,30]. In patients with potential viral infections resulting in COPD exacerbation, particularly SARS-CoV-2, nebulized medications should ideally be avoided or limited to use in negative pressure rooms in order to decrease disease spread.

  Placebo-controlled trials are lacking for SABAs in acute COPD exacerbation, so the main evidence comes from long-term clinical experience and extrapolation from the treatment of asthma and stable COPD. Increasing the dose of nebulized albuterol to 5 mg does not have a significant benefit on spirometry or clinical outcomes [31]. Similarly, continuously nebulized beta-agonists have not been shown to confer an advantage in COPD and may increase adverse effects.

  It is not known whether a rapid-onset, long-acting beta-agonist, like indacaterol, would be a reasonable substitute for albuterol nebulizer treatments in patients not already using indacaterol [32].

Magnesium sulfate — For patients who present with a severe exacerbation that is not responding promptly to short-acting inhaled bronchodilators, we suggest intravenous administration of a single dose of magnesium sulfate (2 g infused over 20 minutes). Intravenous magnesium sulfate has bronchodilator activity thought to arise from inhibition of calcium influx into airway smooth muscle cells [33]. The best evidence for benefit in COPD exacerbations comes from a systematic review (3 studies, 170 participants) that found a decrease in hospitalizations with intravenous magnesium compared with placebo (odds ratio [OR] 0.45, 95% CI 0.23-0.88) [34], which is similar to or better than the effect seen in severe

asthma exacerbations [35]. (See "Acute exacerbations of asthma in adults: Emergency department and inpatient management", section on 'Magnesium sulfate'.)

Intravenous magnesium has an excellent safety profile; however, it is contraindicated in the presence of renal insufficiency, and hypermagnesemia can result in muscle weakness. (See "Hypermagnesemia: Causes, symptoms, and treatment", section on 'Symptoms of hypermagnesemia'.)

Continuing long-acting bronchodilators — While continuation of ongoing therapy with long-acting beta agonists (LABAs) and/or long-acting muscarinic agents (LAMAs) has not been specifically studied, the GOLD strategy advises their continuation during exacerbations [1].

Glucocorticoids in moderate to severe exacerbations — For patients requiring emergency department or hospital-based treatment for a COPD exacerbation, we recommend a course of systemic glucocorticoids.

- **Route** – Oral glucocorticoids are rapidly absorbed (peak serum levels achieved at one hour after ingestion) with virtually complete bioavailability and appear equally efficacious to intravenous glucocorticoids for treating most exacerbations of COPD [11,36,37]. In a systematic review, parenteral glucocorticoids were compared with oral glucocorticoids and no significant differences were noted in the primary outcomes of treatment failure, relapse, or mortality or for any secondary outcomes [36]. However, intravenous glucocorticoids are typically administered to patients who present with a severe exacerbation, who have not responded to oral glucocorticoids at home, who are unable to take oral medication, or who may have impaired absorption due to decreased splanchnic perfusion (eg, patients in shock).

- **Dose** – The optimal dose of systemic glucocorticoids for treating a COPD exacerbation is unknown [1,11]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advise using the equivalent of prednisone 40 mg once daily for the majority of COPD exacerbations (table 2) [1]. Frequently used regimens range from prednisone 30 to 60 mg, once daily, to methylprednisolone 60 to 125 mg, two to four times daily, depending on the severity of the exacerbation [22,37,38]. A growing body of evidence favors using a moderate, rather than high dose of glucocorticoids, for most patients with an exacerbation of COPD. As an example, a comparative analysis of glucocorticoid dosing examined outcomes of 79,985 patients admitted to the hospital with an exacerbation of COPD, excluding those requiring intensive care [38]. The median glucocorticoid dose administered in the first two days was 60 mg for those on oral therapy and 556 mg for intravenous therapy. The risk of treatment failure was no greater with the lower dose. As

this was an observational study and did not include objective measures of airflow limitation, it is possible that less ill patients were more likely to receive oral treatment.

On the other hand, for patients with impending or actual acute respiratory failure due to a COPD exacerbation, many clinicians use an intravenous formulation at a higher dose, such as the equivalent of methylprednisolone 60 mg intravenously, one to four times daily, although outcomes data to support this practice are limited. In an observational cohort study, among 17,239 patients admitted to an intensive care unit with an exacerbation of COPD, a dose of methylprednisolone of 240 mg/day or less, compared with a higher dose (methylprednisolone >240 mg/day), was not associated with a mortality benefit, but was associated with slightly shorter hospital (-0.44 days; 95% CI -0.67 to -0.21) and ICU (-0.31 days; 95% CI -0.46 to -0.16) lengths of stay [39]. Length of mechanical ventilation and need for insulin therapy were also lower in the lower dose group. As this was an observational study, further research is needed to determine the optimal glucocorticoid dose in this setting.

- **Duration** – The optimal duration of systemic glucocorticoid therapy is not clearly established and often depends on the severity of the exacerbation and the observed response to therapy [1,11,40-42]. The GOLD guidelines suggest that glucocorticoids (eg, prednisone 30 to 40 mg/day) be given for five days [1], while the European Respiratory Society/American Thoracic Society guidelines suggest a course of therapy up to 14 days in duration [11]. Thus, a range of 5 to 14 days appears reasonable.

  - Data in support of a 14-day course, rather than a longer duration, come from the Systemic Corticosteroids in COPD Exacerbations (SCCOPE) trial, which compared two and eight week regimens and did not find any additional benefit to the longer course [43]. Patients in the eight week group experienced more glucocorticoid-related side effects.

  - Other studies have examined whether courses shorter than 14 days are also effective for COPD exacerbations. As an example, the Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial randomly assigned 314 patients with exacerbations of COPD, of whom 289 required hospitalization, to prednisone 40 mg daily for 5 or 14 days [22]. No difference was noted in the time to the next exacerbation, the likelihood of an exacerbation in the subsequent 180 days, or the recovery of lung function. The mean cumulative prednisone dose was significantly higher in the 14-day group, but treatment-related adverse effects, such as hyperglycemia and hypertension, were not different between the groups. While this study suggests that a five-day course may be

comparable to 14 days for many patients, further study is needed to determine whether some patients might do better with the longer course.

- A systematic review compared different durations of systemic glucocorticoid therapy (eight studies, 457 participants) and found no difference in the risk of treatment failure with courses of three to seven days compared with longer courses of 10 to 15 days (OR 1.04, 95% CI 0.70-1.56) [40]. Including the data from the REDUCE trial above, the systematic review concluded that a five-day course of oral glucocorticoids is probably comparable to a 14-day or longer course, but that further research is needed to conclude equivalence.

  At the end of the treatment course, glucocorticoid therapy may be discontinued rather than tapered, if the patient has substantially recovered. Alternatively, the dose is tapered over another seven days, as a trial to determine whether a longer course of glucocorticoid therapy is required. However, long-term systemic glucocorticoids should rarely be used for stable COPD if therapy is otherwise optimized. Tapering solely because of concerns about adrenal suppression is not necessary if the duration of therapy is less than three weeks (a duration too brief to cause adrenal atrophy). (See "Glucocorticoid withdrawal", section on 'Recommended tapering regimen' and "Management of refractory chronic obstructive pulmonary disease", section on 'The limited role for systemic glucocorticoids in refractory disease'.)

- **Efficacy** – Systemic glucocorticoids, when added to the bronchodilator therapies described above, improve symptoms and lung function, and decrease the length of hospital stay [1,22,36,43,44]. In a systematic review and meta-analysis of nine studies (n = 917), systemic glucocorticoids reduced the risk of treatment failure by over 50 percent compared with placebo (OR 0.48, 95% CI 0.35-0.67) and, in two studies (n = 415), reduced the risk of relapse at one month (hazard ratio 0.78, 95% CI 0.63-0.97) [36]. For each nine treated subjects, one treatment failure was avoided. The forced expiratory volume in one second (FEV_1) showed significant improvement in the glucocorticoid group up to 72 hours after initiation, but not after that time point. Hospital stay was significantly shorter with glucocorticoid treatment (mean difference -1.22 days, 95% CI -2.26 to -0.18). Mortality up to 30 days was not decreased by systemic glucocorticoids. The risk of hyperglycemia was significantly increased with glucocorticoids compared with placebo (odds ratio 2.79, 95% CI 1.86-4.19).

  Preliminary evidence suggests that using total serum eosinophil counts to guide systemic glucocorticoid therapy may reduce the duration of glucocorticoid exposure [19]. After an initial intravenous dose of methylprednisolone 80 mg, subsequent doses were only given

when the eosinophil count was ≥0.3 x10^9/L. Further study of this strategy is needed prior to implementation.

- **Adverse events** – Even short courses of systemic glucocorticoids are associated with an increased risk of harm, such as hyperglycemia, pneumonia, sepsis, venous thromboembolism, and fracture. The adverse effects of systemic glucocorticoids and their mitigation are discussed separately. (See "Major adverse effects of systemic glucocorticoids".)

Antiviral and antimicrobial agents — Most clinical practice guidelines recommend antibiotics for patients having a moderate to severe COPD exacerbation that requires hospitalization [1,11,45]. The optimal antibiotic regimen for the treatment of exacerbations of COPD has not been determined. We use a "risk stratification" approach when selecting initial antibiotic therapy, providing a broader antibiotic regimen for patients at risk for resistant organisms (algorithm 3). The rationale, diagnosis, and treatment of infection in exacerbations of COPD, including antibiotic selection, are discussed separately. (See "Management of infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations' and "Evaluation for infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations'.)

Antiviral therapy is recommended for patients with clinical and laboratory evidence of influenza infection who require hospitalization for an exacerbation of COPD. Because of the risk of acute bronchoconstriction with inhalation of zanamivir, oseltamivir is preferred unless local resistance patterns suggest a likelihood of oseltamivir-resistant influenza. Antiviral treatment of influenza is discussed in greater detail separately. (See "Seasonal influenza in nonpregnant adults: Treatment".)

Information regarding antiviral resistance that emerges during the influenza season is available through the United States Centers for Disease Control and Prevention. Clinicians should review antiviral resistance patterns for updated antiviral recommendations should resistant strains emerge.

COPD is associated with a greater likelihood of intensive care unit admission, mechanical ventilation, or death among patients with COVID-19 due to SARS-CoV-2 [46-48]. Potential treatments for hospitalized patients with SARS-coronavirus-2 infection (COVID-19) are discussed separately. (See "COVID-19: Management in hospitalized adults" and "COVID-19: Management of the intubated adult".)

Supportive and palliative care — Supportive care for patients hospitalized with an exacerbation of COPD includes the following therapies, as needed:

General measures

- **Cigarette smoking cessation** – Hospitalization can sometimes provide an opportunity for patients who continue to smoke to move towards cigarette smoking cessation. Nicotine replacement therapy can help reduce symptoms of nicotine withdrawal during hospitalization. (See "Overview of smoking cessation management in adults", section on 'Hospitalized patients' and "Pharmacotherapy for smoking cessation in adults".)

- **Thromboprophylaxis** – Hospitalization for exacerbations of COPD increases the risk for deep venous thrombosis and pulmonary embolism [1]. For patients without a risk factor for bleeding who require ICU admission, we recommend pharmacologic thromboprophylaxis; for those not requiring ICU admission, we suggest pharmacologic thromboprophylaxis. Low molecular weight heparin is generally preferred. Preventive measures are discussed in greater detail separately. (See "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults".)

- **Nutritional support** – Oral nutritional supplementation may be of benefit for malnourished patients hospitalized with a COPD exacerbation. (See "Malnutrition in advanced lung disease", section on 'Frequency of malnutrition'.)

Oxygen therapy — Supplemental oxygen is a critical component of acute therapy. Administration of supplemental oxygen should target an SpO_2 of 88 to 92 percent or an arterial oxygen tension (PaO_2) of approximately 60 to 70 mmHg, to minimize the risk of worsening hypercapnia with excess supplemental oxygen [1,26,49]. In two small randomized trials, titrating supplemental oxygen to SpO_2 88 to 92 percent resulted in a lower mortality compared with high-flow (nontitrated) oxygen [49]. (See "The evaluation, diagnosis, and treatment of the adult patient with acute hypercapnic respiratory failure".)

There are numerous devices available to deliver supplemental oxygen during an exacerbation of COPD:

- Venturi masks permit a precise upper limit for the FiO_2, which may be preferable for patients at risk of hypercapnia. Venturi masks can deliver an FiO_2 of 24, 28, 31, 35, 40, or 60 percent.

- Nasal cannula can provide flow rates up to 6 L per minute with an associated FiO_2 of approximately 40 percent (table 3). They are more comfortable and convenient for the patient, especially during oral feedings.

- When a higher FiO_2 is needed, simple facemasks can provide an FiO_2 up to 55 percent using flow rates of 6 to 10 L per minute. However, variations in minute ventilation and inconsistent entrainment of room air affect the FiO_2 when simple facemasks (or nasal cannula) are used.

- Non-rebreathing masks with a reservoir, one-way valves, and a tight face seal can deliver an inspired oxygen concentration up to 90 percent, but are generally not needed in this setting.

- High-flow nasal cannula (HFNC) provide supplemental oxygen (adjustable FiO_2) at a high flow rate (up to 60 L/min that results in a low level of continuous positive airway pressure. The specific indications for HFNC remain unclear, and robust comparisons of HFNC with noninvasive ventilation (NIV) in patients with COPD exacerbations are lacking [1,50,51]. (See "Heated and humidified high-flow nasal oxygen in adults: Practical considerations and potential applications".)

A high FiO_2 is generally not required to correct the hypoxemia associated with exacerbations of COPD. Inability to correct hypoxemia with a relatively low FiO_2 (eg, 4 L/min by nasal cannula or 35 percent by mask) should prompt consideration of an additional cause of hypoxemia, such as pulmonary emboli, acute respiratory distress syndrome, pulmonary edema, or severe pneumonia. (See "Measures of oxygenation and mechanisms of hypoxemia".)

Adequate oxygenation (ie, to achieve an oxygen saturation of 88 to 92 percent) must be assured, even if it leads to acute hypercapnia. Hypercapnia is generally well tolerated in patients whose $PaCO_2$ is chronically elevated. However, mechanical ventilation may be required if hypercapnia is associated with depressed mental status, profound acidemia, or cardiac dysrhythmias. (See 'Ventilatory support' below and "The evaluation, diagnosis, and treatment of the adult patient with acute hypercapnic respiratory failure" and "Adverse effects of supplemental oxygen", section on 'Accentuation of hypercapnia'.)

Compared with oxygen-driven nebulization, air-driven nebulization of inhaled medications is less likely to cause an increase in $PaCO_2$ and is therefore preferred [30]. (See 'Hospital-based bronchodilator therapies' above.)

Ventilatory support — For patients who fail supportive therapy with oxygen and medications, ventilatory support is necessary assuming this is consistent with the patient's goals of care (see 'Palliative care' below). HFNC is not routinely administered in patients with acute exacerbations of COPD, although some experts administer it cautiously in this population prior to the application of NIV. (See "Heated and humidified high-flow nasal oxygen in adults: Practical considerations and potential applications".)

- **Noninvasive ventilation** – NIV (also known as noninvasive positive pressure ventilation [NPPV]) refers to mechanical ventilation delivered through a noninvasive interface, such as a face mask, nasal mask, orofacial mask, or nasal prongs (nasal pillows). NIV reduces mortality and the intubation rate and is the preferred method of ventilatory support in many patients with an exacerbation of COPD [11].

  Most commonly, NIV is initiated in the emergency department, intensive care unit (ICU), or a specialized respiratory unit to enable close monitoring, although this has not been formally studied and varies among hospitals. Patients who develop acute or acute-on-chronic respiratory acidosis (as characterized frequently by $PaCO_2$ >45 mmHg [6 kPa] and pH <7.35) are the subgroup who are most likely to benefit from an initial trial of NIV. Bilevel positive airway pressure is typically used. For other patients with nonhypercapnic respiratory failure due to COPD exacerbation, a trial of NIV is also appropriate, although the derived benefit may be considerably less. (See "Noninvasive ventilation in adults with acute respiratory failure: Benefits and contraindications".)

  A reasonable approach is to initiate bilevel NIV in a spontaneously triggered mode with a backup respiratory rate (eg, 8 breaths/minute); typical initial settings include an inspiratory positive airway pressure (IPAP) of 8 to 12 cm H_2O and an expiratory pressure (EPAP) of 3 to 5 cm H_2O. NIV is discussed in detail separately. (See "Noninvasive ventilation in adults with acute respiratory failure: Practical aspects of initiation".)

- **Invasive ventilation** – Invasive mechanical ventilation should be administered when patients fail NIV, do not tolerate NIV, or have contraindications to NIV. Invasive mechanical ventilation for acute respiratory failure due to a COPD exacerbation is discussed separately. (See "Invasive mechanical ventilation in acute respiratory failure complicating chronic obstructive pulmonary disease".)

Palliative care — The goals of palliative care are to prevent and relieve suffering and aid in the end-of-life care of patients with advanced disease. Some patients may have had a goals of care discussion with their physician and will have an advance directive in place. For those who do not have an advance directive, it is helpful for patients, their families, and their healthcare providers to review the patient's understanding of their diagnosis and expected disease course, and then reflect on the patient's goals, values, and beliefs. This information is used to inform decision-making in the context of care that is medically reasonable and appropriate. (See "Discussing goals of care" and "Advance care planning and advance directives" and "Palliative care for adults with nonmalignant chronic lung disease" and "Palliative care: Issues in the intensive care unit in adults".)

For patients with COPD, an important component of decision-making is whether intubation and mechanical ventilation are appropriate and desirable in the event of respiratory failure. When discussing a potential trial of mechanical ventilation for an exacerbation of COPD, parameters for discontinuing mechanical ventilation should be included. The potential outcomes of intubation/mechanical ventilation should be described to help the patient's decision-making. While prognostic uncertainty and variable trajectory of illness make communication about these issues difficult [52], it is important to incorporate this uncertainty into advance care planning.

Given the high one-year mortality rate after hospitalization for a COPD exacerbation, it may be appropriate to consider a palliative care referral during or shortly after a hospitalization for COPD. Palliative care consultation can help explore the patient's understanding of their illness and prognosis, assess and manage symptoms (eg, dyspnea, anxiety, panic, depression), discuss the patient's goals of care, place of death preferences, and advance directives, and help implement end-of-life care. (See "Palliative care for adults with nonmalignant chronic lung disease" and "Assessment and management of dyspnea in palliative care".)

Adjusting therapy for poor response — Assess several potential contributors:

- Optimize schedule for delivery of inhaled medications to ensure doses are not being missed.
- Ask patients about continued smoking and discuss ways to reduce or stop smoking.
- Evaluate for conditions that might contribute to or mimic symptoms and signs of a COPD exacerbation, such as viral respiratory tract infection, pneumonia, pulmonary emboli, pneumothorax, heart failure, dysrhythmias, tracheomalacia, diaphragmatic dysfunction, and intraabdominal processes limiting diaphragmatic excursion. Testing may include complete blood count and differential, serum brain natriuretic peptide, microbiologic testing, lower extremity compression ultrasonography for deep venous thrombosis, transthoracic echocardiogram, chest radiograph, and/or computed tomography with or without pulmonary angiography. (See "COPD exacerbations: Clinical manifestations and evaluation", section on 'Differential diagnosis'.)

Discharge planning — It is hoped that comprehensive discharge planning will help speed symptom resolution and reduce readmissions for COPD exacerbations. However, the optimal components of discharge planning have not been determined, so discharge-related decision-making is largely guided by good medical practice, as described separately. (See "COPD exacerbations: Prognosis, discharge planning, and prevention".)

A meta-analysis of 13 randomized controlled trials of pulmonary rehabilitation within four weeks of hospitalization for acute exacerbation of COPD showed benefits of reduced mortality and hospital readmissions and enhanced healthcare-related quality of life and walking distance [53].

TREATMENTS WITHOUT DOCUMENTED BENEFIT

Mucoactive agents, methylxanthines, and mechanical techniques to augment sputum clearance have not been shown to confer benefit for patients with a COPD exacerbation.

- Mucoactive agents – There is little evidence supporting the use of mucoactive agents (eg, N-acetylcysteine) in exacerbations of COPD [54-56]. Some mucoactive agents may worsen bronchospasm. (See "Role of mucoactive agents and secretion clearance techniques in COPD".)

  The lack of efficacy of mucoactive agents in the treatment of COPD exacerbations was best demonstrated by a double-blind trial that randomly assigned 50 patients with a COPD exacerbation to receive N-acetylcysteine (600 mg, twice daily) or placebo for seven days [56]. There was no difference in the rate of change of forced expiratory volume in one second (FEV_1), vital capacity, oxygen saturation, breathlessness, or length of stay between the two groups.

- Methylxanthines – The methylxanthines, aminophylline and theophylline, are considered second-line therapy for exacerbations of COPD [1]. Randomized trials of intravenous aminophylline in this setting have failed to show efficacy beyond that induced by inhaled bronchodilator and glucocorticoid therapy. In addition to lack of efficacy, methylxanthines caused significantly more nausea and vomiting than placebo and trended toward more frequent tremor, palpitations, and arrhythmias.

- Nebulized magnesium – Nebulized isotonic magnesium (151 mg per dose) had no effect on FEV_1 when added to nebulized salbutamol (albuterol) in one study of patients with exacerbations of COPD [57]. A subsequent systematic review including four additional studies found no effect of nebulized magnesium on hospital admission or the need for invasive or noninvasive breathing support [34].

- Chest physiotherapy – Mechanical techniques to augment sputum clearance, such as directed coughing, chest physiotherapy with percussion and vibration, intermittent positive pressure breathing, and postural drainage, have not been shown to be beneficial

in COPD and may provoke bronchoconstriction. Their use in exacerbations of COPD (in the absence of bronchiectasis) is not supported by clinical trials [1,54,55].

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" and "Society guideline links: Pulmonary rehabilitation".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Chronic bronchitis (The Basics)" and "Patient education: Medicines for COPD (The Basics)")
- Beyond the Basics topics (see "Patient education: Chronic obstructive pulmonary disease (COPD) treatments (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Triage and goals of therapy** – A COPD exacerbation is characterized by dyspnea and/or cough and sputum that worsens over ≤14 days; it may be accompanied by tachypnea and/or tachycardia and is often associated with increased local and systemic inflammation caused by airway infection, pulmonary embolism, pollution, or other airway insult. (See 'Introduction' above.)

Triage to determine site of care is based on signs and symptoms, vital signs, arterial blood gas (ABG), and response to initial office/emergency department care (algorithm 1). (See 'Triage to home or hospital' above.)

Regardless of treatment location, management goals are to:

- Reverse airflow limitation using short-acting inhaled bronchodilators and systemic glucocorticoids
- Treat infection, which is implicated in most exacerbations
- Exclude other causes for which additional therapy is needed (eg, pulmonary embolism)
- Ensure appropriate oxygenation
- Avert intubation and mechanical ventilation

- **Rapid overview of management for severe exacerbations** – A rapid overview for the evaluation and management of severe exacerbations of chronic obstructive pulmonary disease (COPD) in the emergency department is provided in the table (table 1). (See 'Emergency department and hospital management' above.)

- **Short-acting bronchodilators** – For all patients having a COPD exacerbation, we recommend inhaled short-acting bronchodilator therapy (**Grade 1B**).

  - At home, patients should use their prescribed reliever medication, typically a short-acting beta-agonist (SABA; eg, albuterol, levalbuterol) or combined SABA plus short-acting muscarinic antagonist (SAMA; eg, ipratropium) (algorithm 4). (See 'Home/office short-acting bronchodilator treatments' above.)

  - In outpatient clinics and hospital settings, we suggest administration of SABA-SAMA combination therapy rather than SABA alone (**Grade 2C**). The combination is well tolerated and might achieve better bronchodilation. (See 'Hospital-based bronchodilator therapies' above.)

  - We prefer nebulized therapy for reliable airway delivery, but delivery by soft mist inhaler (SMI), dry-powder inhaler (DPI), or metered dose inhaler (MDI) with spacer is equally effective when properly administered.

  The usual dose for acute symptom relief is two puffs (MDI/DPI), one inhalation (SMI), or 3 mL (nebulization solution) every 20 to 60 minutes for two to three doses, then every two to four hours based on the patient response. Standard solutions for nebulization contain 2.5 mg of albuterol with or without 0.5 mg of ipratropium in 3 mL sterile normal saline. (See

'Home/office short-acting bronchodilator treatments' above and 'Hospital-based bronchodilator therapies' above.)

For patients in emergency room or inpatient settings with limited benefit from short-acting inhaled bronchodilators, we suggest intravenous magnesium (**Grade 2C**). (See 'Magnesium sulfate' above.)

- **Systemic glucocorticoids** – For patients hospitalized due to an acute exacerbation of COPD, we recommend a course of systemic glucocorticoids (**Grade 1B**); we also suggest glucocorticoids for patients who do not require hospitalization (**Grade 2B**). A reasonable dose for most patients is prednisone 40 to 60 mg once daily (or the equivalent) for 5 to 14 days. A higher dose of glucocorticoids may occasionally be used in patients with impending or actual respiratory failure. In general, results with oral dosing are similar to those with intravenous dosing. (See 'Home oral glucocorticoid therapy' above and 'Glucocorticoids in moderate to severe exacerbations' above.)

- **Antibiotics and antiviral agents** – Antibiotics are indicated for many patients having a COPD exacerbation, particularly those who require hospitalization for their exacerbation (algorithm 2 and algorithm 3). Antiviral therapy may be appropriate for some infections triggered by respiratory viruses. (See 'Antimicrobial therapy, in selected outpatients' above and 'Antiviral and antimicrobial agents' above and "Management of infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations'.)

- **Titrating supplemental oxygen** – Patients with hypoxemia due to an exacerbation of COPD should receive supplemental oxygen (algorithm 1). We suggest that supplemental oxygen be titrated to a target of 88 to 92 percent pulse oxygen saturation, rather than using high-flow, nontitrated oxygen (**Grade 2B**). Lower oxygen targets may both improve monitoring for and prevent worsening of hypercapnia. (See 'Oxygen therapy' above.)

- **Ventilatory support** – Ventilatory support is necessary for patients who develop respiratory fatigue despite supportive therapy with medications and oxygen (algorithm 1). Noninvasive ventilation (NIV) is the preferred method in most patients. (See 'Ventilatory support' above and "Noninvasive ventilation in adults with acute respiratory failure: Benefits and contraindications", section on 'Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with hypercapnic respiratory acidosis'.)

  Invasive mechanical ventilation is required in patients with respiratory failure despite NIV, who do not tolerate NIV, or who have contraindications to NIV. (See 'Ventilatory support'

above and "Invasive mechanical ventilation in acute respiratory failure complicating chronic obstructive pulmonary disease".)

- **Treatments without clear benefit** – Mucoactive agents, methylxanthines, and mechanical techniques to augment sputum clearance have not been shown to confer benefit for COPD exacerbations. (See 'Treatments without documented benefit' above.)

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Topic 1461 Version 85.0

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

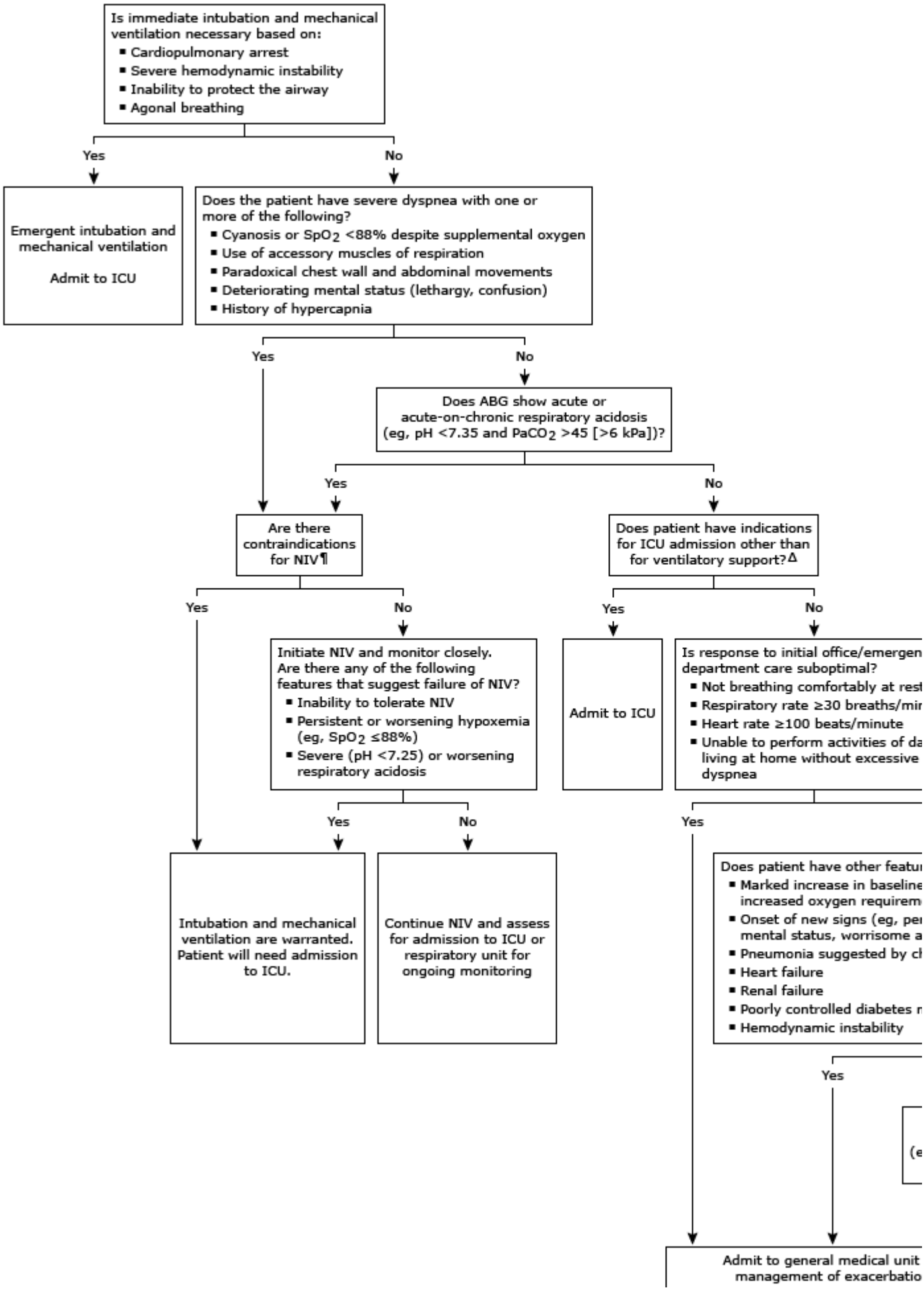
of resistance).
▪ No *Pseudomonas* risk factor(s)¶: Ceftriaxone 1 to 2 grams IV, **or** cefotaxime 1 to 2 grams IV, **or** levofloxacin 500 mg IV or orally, **or** moxifloxacin 400 mg IV or orally
▪ *Pseudomonas* risk factor(s)¶: Piperacillin-tazobactam 4.5 grams IV, **or** cefepime 2 grams IV, **or** 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.

Algorithm for triage of patients presenting with COPD exacerbation*


Is immediate intubation and mechanical ventilation necessary based on:
Cardiopulmonary arrest
Severe hemodynamic instability
Inability to protect the airway
Agonal breathing
Yes
No
Emergent intubation and mechanical ventilation
Admit to ICU
Does the patient have severe dyspnea with one or more of the following?
Cyanosis or SpO2 <88% despite supplemental oxygen
Use of accessory muscles of respiration
Paradoxical chest wall and abdominal movements
Deteriorating mental status (lethargy, confusion)
History of hypercapnia
Yes
No
Does ABG show acute or acute-on-chronic respiratory acidosis (eg, pH <7.35 and PaCO2 >45 [>6 kPa])?
Yes
No
Are there contraindications for NIV¶
Does patient have indications for ICU admission other than for ventilatory support?Δ
Yes
No
Yes
No
Initiate NIV and monitor closely. Are there any of the following features that suggest failure of NIV?
Inability to tolerate NIV
Persistent or worsening hypoxemia (eg, SpO2 ≤88%)
Severe (pH <7.25) or worsening respiratory acidosis
Admit to ICU
Is response to initial office/emergen department care suboptimal?
Not breathing comfortably at rest
Respiratory rate ≥30 breaths/min
Heart rate ≥100 beats/minute
Unable to perform activities of da living at home without excessive dyspnea
Yes
No
Yes
Intubation and mechanical ventilation are warranted. Patient will need admission to ICU.
Continue NIV and assess for admission to ICU or respiratory unit for ongoing monitoring
Does patient have other featu
Marked increase in baseline increased oxygen requirem
Onset of new signs (eg, per mental status, worrisome a
Pneumonia suggested by ch
Heart failure
Renal failure
Poorly controlled diabetes m
Hemodynamic instability
Yes
(e
Admit to general medical unit management of exacerbatio

COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; SpO_2: pulse oxygen saturation; NIV: noninvasive positive pressure ventilation via nasal mask, face mask, or nasal plugs; ABG: arterial blood gas; $PaCO_2$: arterial tension of carbon dioxide; FEV_1: forced expiratory volume in one second; PaO_2: arterial oxygen tension.

* This algorithm can be used to support decisions regarding hospitalization and ventilatory support, but clinical judgment should be employed in all cases. Prior goals of care and advance care planning discussions should be reviewed to ensure that decisions, particularly about invasive ventilation, are consistent with the patient's values and preferences. Short-acting bronchodilators should be given during triage assessment; symptomatic improvement with bronchodilator administration may impact triage decisions.

¶ Contraindications to NIV:

- Inability to protect the airway or clear secretions
- Severely impaired consciousness
- Nonrespiratory organ failure that is acutely life-threatening
- High aspiration risk
- Inability to cooperate
- Facial surgery, trauma, or deformity
- Recent esophageal anastomosis

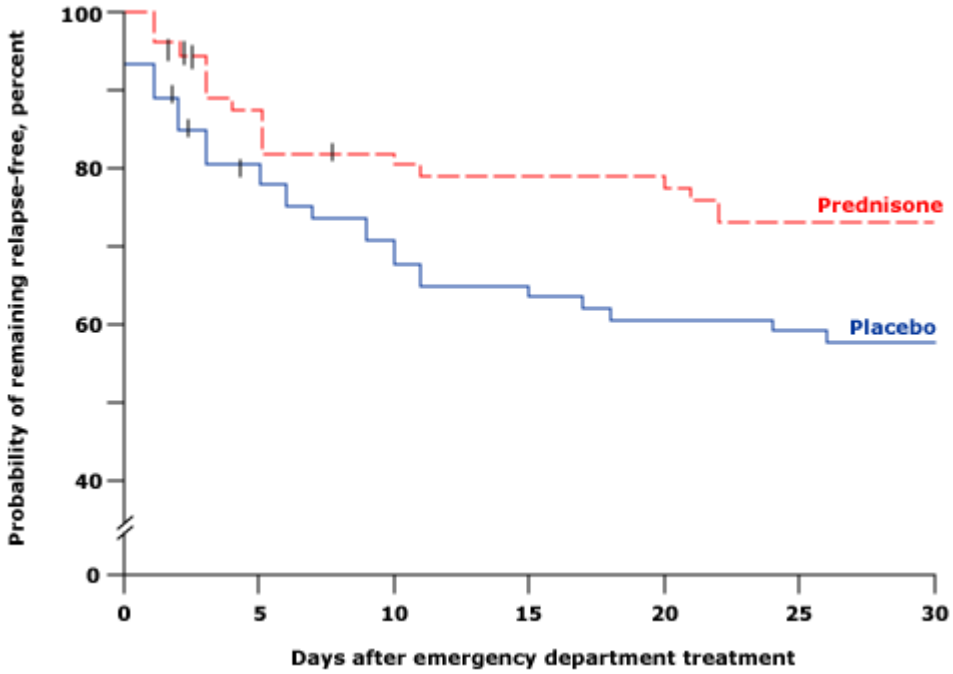
Δ Indications for ICU admission vary among institutions and generally include (but are not limited to) the following:

- Hemodynamic instability requiring vasopressor support
- Unstable cardiac events (eg, acute myocardial infarction, complex arrhythmias, cardiogenic shock)
- Severe neurologic complications (eg, major acute intracranial hemorrhage or stroke, status epilepticus)
- Persistent or worsening hypoxemia (eg, PaO_2 <50 mmHg [6.62 kPa] despite supplemental oxygen)
- Need for monitoring or nursing care that exceeds the capacity of non-ICU settings

◇ Severe airflow limitation, a history of frequent or severe exacerbations, and frailty are additional factors that may be associated with increased risk for severe exacerbation.

Graphic 114160 Version 3.0

Kaplan-Meier estimates of the probability of remaining relapse-free at 30 days for outpatients with acute exacerbations of COPD treated with prednisone or placebo

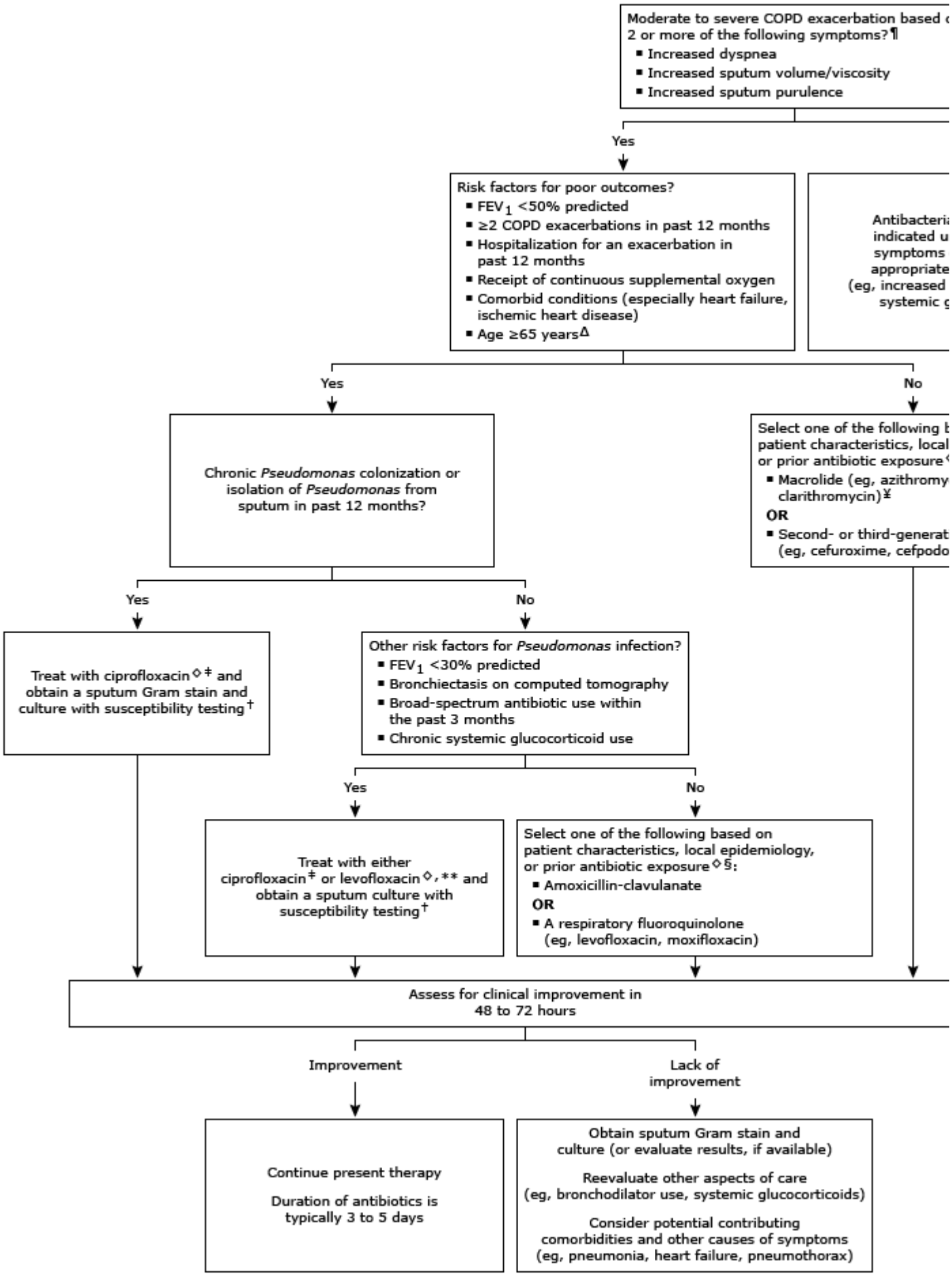


Tick marks represent censored data. p=0.04 by the log-rank test.

Data from: N Engl J Med 2003; 348:2623.

Graphic 60719 Version 1.0

Our approach to empiric antibacterial treatment of COPD exacerbations in outpatients*


Moderate to severe COPD exacerbation based
2 or more of the following symptoms?¶
Increased dyspnea
Increased sputum volume/viscosity
Increased sputum purulence
Yes
Risk factors for poor outcomes?
FEV1 <50% predicted
≥2 COPD exacerbations in past 12 months
Hospitalization for an exacerbation in past 12 months
Receipt of continuous supplemental oxygen
Comorbid conditions (especially heart failure, ischemic heart disease)
Age ≥65 years△
Antibacteri
indicated u
symptoms
appropriate
(eg, increased
systemic g
Yes
No
Chronic Pseudomonas colonization or isolation of Pseudomonas from sputum in past 12 months?
Select one of the following b
patient characteristics, local
or prior antibiotic exposure
Macrolide (eg, azithromy
clarithromycin)¥
OR
Second- or third-generat
(eg, cefuroxime, cefpodo
Yes
No
Treat with ciprofloxacin◇‡ and obtain a sputum Gram stain and culture with susceptibility testing†
Other risk factors for Pseudomonas infection?
FEV1 <30% predicted
Bronchiectasis on computed tomography
Broad-spectrum antibiotic use within the past 3 months
Chronic systemic glucocorticoid use
Yes
No
Treat with either ciprofloxacin‡ or levofloxacin◇,** and obtain a sputum culture with susceptibility testing†
Select one of the following based on patient characteristics, local epidemiology, or prior antibiotic exposure◇§:
Amoxicillin-clavulanate
OR
A respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin)
Assess for clinical improvement in 48 to 72 hours
Improvement
Lack of improvement
Continue present therapy
Duration of antibiotics is typically 3 to 5 days
Obtain sputum Gram stain and culture (or evaluate results, if available)
Reevaluate other aspects of care (eg, bronchodilator use, systemic glucocorticoids)
Consider potential contributing comorbidities and other causes of symptoms (eg, pneumonia, heart failure, pneumothorax)

Prompt and appropriate antibiotic use has been associated with improved clinical outcomes in patients with moderate to severe COPD exacerbations. Empiric regimens are designed to target the most likely pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*) and should be broadened to target drug-resistant pathogens and difficult-to-eradicate pathogens (eg, macrolide-resistant *S. pneumoniae*, nontypeable strains of *H. influenzae*) in those at risk for poor outcomes. Coverage for *Pseudomonas* is indicated in patients with risk factors for infection with this pathogen. All patients should be evaluated for clinical response in approximately 72 hours, and sputum Gram stain and culture should be considered for those who fail to response to empiric treatment. Modifications to this approach may be needed for patients with a history of colonization or infection with drug-resistant pathogens (including *Pseudomonas*) or when a specific pathogen is suspected.

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

* Antiviral therapy for influenza is also indicated for exacerbations triggered by influenza infection.

¶ Suspicion for other cardiopulmonary disorders (heart failure, pneumothorax) and more severe infections (eg, pneumonia) should be absent for the diagnosis of an acute COPD exacerbation.

Δ Age alone is not a strict risk factor but should be considered as additive to other risk factors.

◇ Selection among antibiotic choices is based on local microbial sensitivity patterns, patient comorbidities, prior infecting organisms, potential adverse events and drug interactions, and also provider and patient preferences. In particularly, modifications to this regimen may be needed for patients with a history of drug-resistant *Pseudomonas* based on severity of illness, degree of suspicion for *Pseudomonas*, and prior susceptibility profiles of pseudomonal isolates.

§ If recent antibiotic exposure (eg, within the past 3 months), select an antibiotic from a different class than the most recent agent used.

¥ Trimethoprim-sulfamethoxazole is a reasonable alternative when macrolides and cephalosporins cannot be used due to allergy, potential adverse effects, or availability.

‡ Some experts add amoxicillin or another agent with better activity against *S. pneumoniae* to ciprofloxacin for broader empiric treatment.

† Because fluoroquinolone resistance is prevalent among *Pseudomonas aeruginosa* strains, we obtain a sputum Gram stain and culture with susceptibility testing for these patients to help guide subsequent management decisions. For most other outpatients, obtaining a sputum culture is not needed unless the patient fails to respond to empiric treatment.

** Levofloxacin has lesser activity against *Pseudomonas* than ciprofloxacin but has greater activity against *S. pneumoniae* and *M. catarrhalis* is thus a reasonable alternative to ciprofloxacin for patients who are at increased risk of *Pseudomonas* infection but lack microbiologic evidence of *Pseudomonas* infection or colonization.

References:

1. *Sethi S, Murphy TF. Acute exacerbations of chronic bronchitis: New developments concerning microbiology and pathophysiology--impact on approaches to risk stratification and therapy. Infect Dis Clin N Am 2004; 18:861.*
2. *Sethi S, Anzueto A, Miravitlles M, et al. Determinants of bacteriological outcomes in exacerbations of chronic obstructive pulmonary disease. Infection 2016; 44:65.*

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.*

Graphic 66357 Version 14.0

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an antiinflammatory effect¶. The typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

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* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

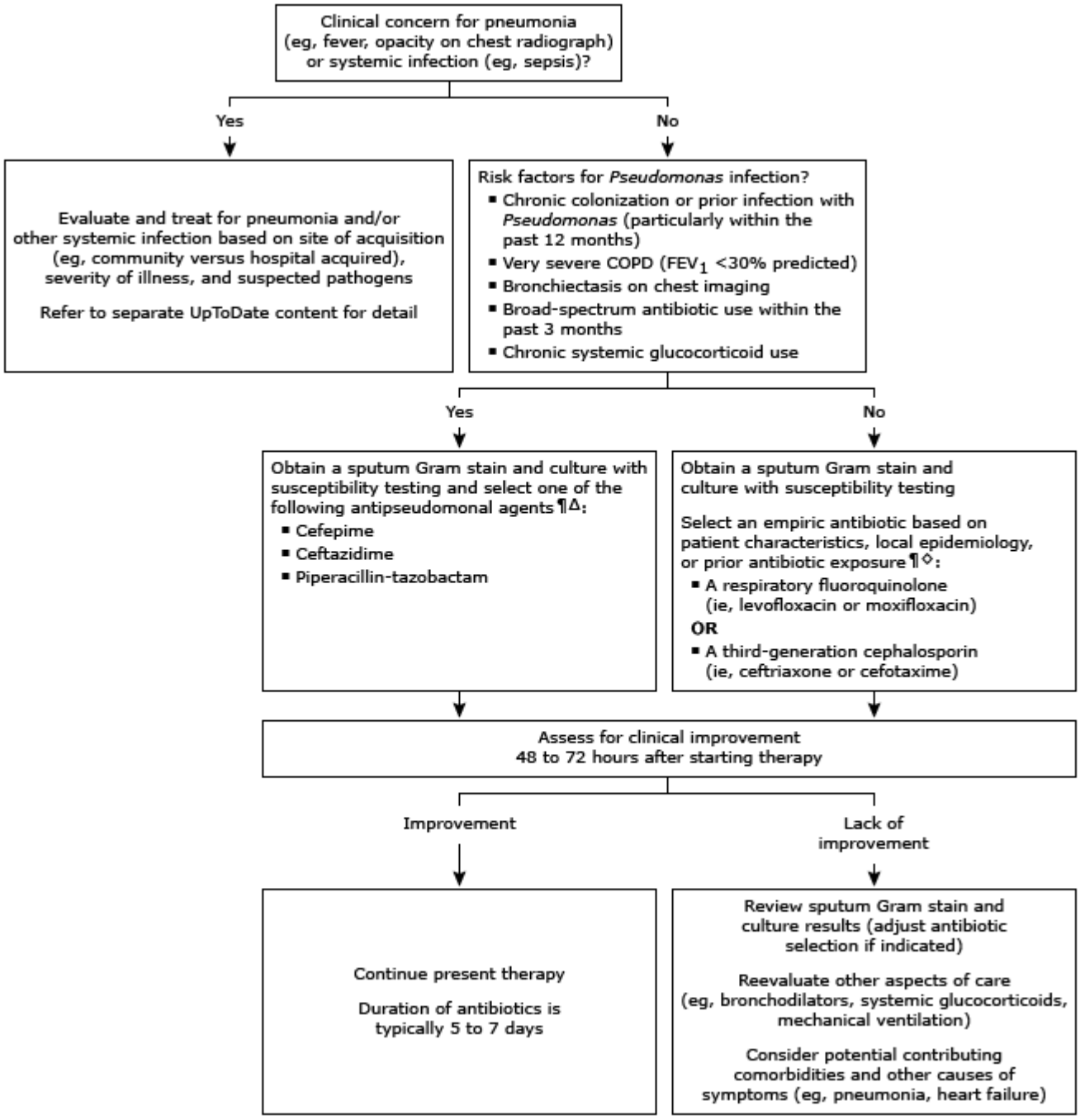
¶ The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is not used clinically as an antiinflammatory agent.

Data from:

1. *Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed, Brunton LL, Chabner BA, Knollmann BC (Eds), McGraw-Hill Education 2011.*
2. *Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 2013, 9:30.*

Graphic 64138 Version 23.0

Our approach to empiric antibacterial treatment of COPD exacerbations in hospitalized patients*



Prompt and appropriate antibiotic use has been associated with improved clinical outcomes in patients hospitalized for COPD exacerbations. Empiric regimens are designed to target the most likely pathogens (*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*). *Pseudomonas* should be targeted in those with risk factors for infection with this pathogen. Generally, a sputum Gram stain and culture with susceptibility testing should be obtained for hospitalized patients. Modifications to the empiric regimen may be needed based on sputum Gram stain and culture results, particularly for patients who do not respond to the initial empiric regimen within 48 to 72 hours of starting treatment.

Modifications to this approach may be needed for patients with a history of colonization or infection with drug-resistant pathogens (including *Pseudomonas*) or when a specific pathogen is suspected.

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

* Antiviral therapy for influenza is also indicated for exacerbations triggered by influenza infection.

¶ Selection among antibiotic choices is based on local microbial sensitivity patterns, patient comorbidities, prior infecting organisms, potential adverse events and drug interactions, and also provider and patient preferences. Modifications to these regimens may be needed for patients with suspicion for specific pathogens and/or history of drug-resistant organisms (eg, drug-resistant *Pseudomonas*).

Δ For those who cannot tolerate these agents, alternatives include ciprofloxacin, aztreonam, certain carbapenems (eg, meropenem, imipenem), and aminoglycosides. We generally select among them based on local epidemiology, prior susceptibility testing results, drug interactions, and patient comorbidities or intolerances. Two agents are often needed for empiric treatment. Refer to the UpToDate content for detail.

◇ If recent antibiotic exposure (eg, within the past 3 months), select an antibiotic from a different class than the most recent agent used.

References:

1. *Sethi S, Murphy TF. Acute exacerbations of chronic bronchitis: New developments concerning microbiology and pathophysiology--impact on approaches to risk stratification and therapy. Infect Dis Clin N Am 2004; 18:861.*
2. *Sethi S, Anzueto A, Miravitlles M, et al. Determinants of bacteriological outcomes in exacerbations of chronic obstructive pulmonary disease. Infection 2016; 44:65.*
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.*

Graphic 53537 Version 13.0

Oxygen delivery systems

System	Percent oxygen delivered*	Indications	Comments
Blow by	Less than 30 percent	Use for spontaneously breathing children who require low doses of oxygen and do not tolerate a mask	Best delivered at a flow rate of at least 10 L/minute through a reservoir (ie, a simple mask or Styrofoam or paper drinking cup with oxygen tubing poked through the bottom) with the reservoir held near the patient's face by a parent or other caregiver
Low flow nasal cannula (1 to 4 L/min)	25 to 40 percent	Use to deliver low-dose oxygen to spontaneously breathing patients	Percent oxygen delivered affected by respiratory rate, tidal volume, and extent of mouth breathing. In infants, limit flow rate to 2 L/min or less to avoid inadvertent administration of positive airway pressure
Simple mask	35 to 50 percent	Use to deliver low-dose oxygen to spontaneously breathing patients	Percent oxygen delivered affected by mask fit and respiratory rate
Small diffuser (OxyMask)	25 to >80 percent	Use to provide low- or high-dose oxygen to spontaneously breathing patients	Range of oxygen delivery at different flow rates (approximately 25 percent at 1.5 L/min to >80 percent at ≥15 L/min). Open-mask design may be better tolerated by children. May provide equivalent oxygen delivery at lower flow rates than other mask devices.
Partial rebreather mask	50 to 60 percent	Use to conserve oxygen	
Nonrebreather mask	65 to 95 percent	Use to deliver high-dose oxygen to spontaneously breathing patients	Tight mask fit required to deliver higher concentrations of oxygen
Hood	30 to 90 percent	Infants less than one year of age	Noisy for patient
Tent	25 to 50 percent	Use for children who require 30 percent oxygen or less	Mist may obscure view of patient. Noisy for patient. Low-flow nasal cannula or masks preferred.

Self-inflating ventilation bag	95 to 100 percent, with reservoir	Use to provide assisted ventilation and oxygen	Do not use to provide blow by. Must use with a reservoir to provide higher oxygen concentrations.
Flow-inflating ventilation bag	100 percent	Use to provide assisted ventilation and oxygen	May use to provide blow by. Requires experience to use reliably.

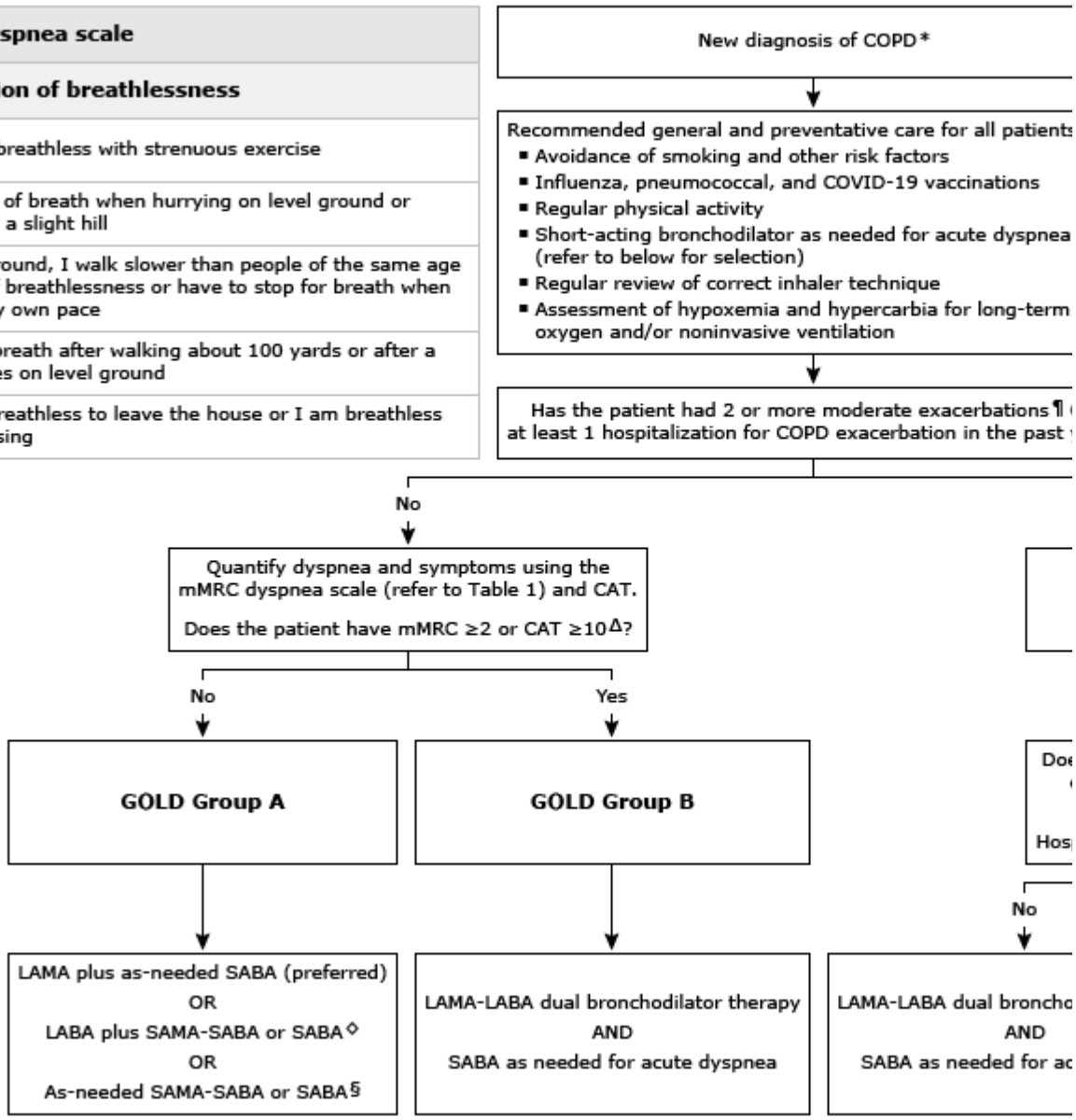
*Actual percent oxygen delivered may vary widely depending on the type of delivery device, device manufacturer, oxygen flow rate provided to the device, and, for oxygen masks, mask fit. All patients receiving supplemental oxygen warrant monitoring with pulse oximetry.

Graphic 60610 Version 9.0

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