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 acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication" [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".)

ADVICE RELATED TO COVID-19

COPD is associated with a greater likelihood of intensive care unit admission, mechanical ventilation, or death among patients with coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3-5].

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.

For patients hospitalized with COVID-19, use of nebulized medications should be avoided or limited to negative pressure rooms because of the risk of aerosolizing SARS-CoV-2 and enhancing disease spread. For patients who use nebulizers at home, caution is advisable to avoid spread of the virus to other members of the household.

Additional information about COVID-19 is provided separately.

- (See "COVID-19: Questions and answers".)
- (See "COVID-19: Management of adults with acute illness in the outpatient setting".)
- (See "COVID-19: Management in hospitalized adults".)
- (See "COVID-19: Management of the intubated adult".)

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) [1,2]. 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 include [1]:

- 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 or signs of respiratory distress
- Severe underlying COPD (eg, forced expiratory volume in one second [FEV_1] ≤50 percent of predicted)
- History of frequent exacerbations or prior hospitalization for exacerbations

- Serious comorbidities including pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal failure, or liver failure
- Frailty
- Insufficient home support

Intensive home care, which generally includes nurse visits, home oxygen, and physical therapy, may be an alternative in certain locations (eg, United Kingdom, Europe) for selected patients with an exacerbation of COPD [6-10]. A meta-analysis of seven trials noted that intensive home care resulted in equivalent clinical outcomes and substantial cost savings compared to hospitalization [11]. 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.

Beta adrenergic agonists — We recommend that all patients with a COPD exacerbation receive inhaled short-acting bronchodilator therapy. 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 [1,12,13].

Albuterol is sometimes combined with an additional short-acting bronchodilator (the short-acting muscarinic antagonist [SAMA] ipratropium) in a soft mist inhaler (SMI). (See 'Muscarinic antagonists' below.)

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 hour 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 'Beta adrenergic agonists' below and "Delivery of inhaled medication in adults", section on 'Home use' and 'Muscarinic antagonists' below.)

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. (See 'Beta adrenergic agonists' above.)

The usual dose of ipratropium for an acute exacerbation of COPD is two inhalations by 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). (See 'Beta adrenergic agonists' above.)

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 [14,15]. However, this finding has not been universal, and other studies not found an additive effect in COPD exacerbations [16,17]. A longer duration of bronchodilation has been observed with the addition of ipratropium to albuterol in stable COPD [18].

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].

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. 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 [1,2,13]. 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 [19]. 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 [20]. 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 'Systemic glucocorticoids' below.)

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 side effects of systemic glucocorticoids".)

Inhaled glucocorticoids — 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 [21,22]. 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 [21].

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 [23].

Antimicrobial therapy

- **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 antibiotics for moderately or severely ill patients with COPD exacerbations who have increased cough and sputum purulence [1]. We vary slightly from the GOLD guidelines in our clinical practices (algorithm 2):

- We recommend antibiotics for outpatients with a moderate or severe exacerbation of COPD, which is defined as having at least two of these three symptoms – increased dyspnea, increased sputum volume, or increased sputum purulence.
- We do **not** initiate antibiotic therapy in patients whose exacerbation is mild, which we define as having only one of these three symptoms and not requiring hospitalization.

- **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 cause symptoms that overlap with a COPD exacerbation. Diagnosis and treatment are discussed separately. (See "COVID-19: Diagnosis" and 'Advice related to COVID-19' above 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 [1,24]. 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]:

- **No respiratory failure** – Respiratory rate 20 to 30 breaths per minute; 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 >30 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 >30 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'.)

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 [1,24,25]. 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 [25]. (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 2). 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 [1,26,27]. (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 [28]. (See 'Beta adrenergic agonists' below.)

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 [12].

  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 respiratory acidosis ($PaCO_2$ >45 mmHg [6 kPa] or pH <7.35) are the subgroup who are most likely to benefit from an initial trial of NIV (typically with bilevel positive airway pressure). 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 [29], 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".)

Initial pharmacologic therapy

Beta adrenergic agonists — 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 [1,2]. These medications may be administered via a nebulizer, metered dose inhaler (MDI) with a spacer device, or dry powder inhaler (DPI) and may be combined with a short-acting muscarinic antagonist (SAMA; eg, ipratropium) [1,14]. (See "Delivery of inhaled medication in adults" and "The use of inhaler devices in adults" and 'Muscarinic antagonists' below.)

- **Dose and administration** – 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 one hour for two to three doses and then every two to four hours as needed, guided by the response to therapy [1].

  In this setting, levalbuterol, which contains one of the enantiomers of albuterol called R-albuterol, is dosed 1.25 mg (diluted to a total of 3 mL with sterile saline) by nebulizer at the same frequency as albuterol. Levalbuterol (45 mcg/actuation) by MDI is given one to two inhalations (most commonly two, occasionally four) every one hour for two to three doses, then every two to four hours as needed. For patients requiring mechanical ventilation, up to eight inhalations may be given if needed.

  Increasing the dose of nebulized albuterol to 5 mg does not have a significant benefit on spirometry or clinical outcomes [30]. Similarly, continuously nebulized beta agonists have not been shown to confer an advantage in COPD and may increase adverse effects. When combined with ipratropium, albuterol 2.5 mg is mixed with ipratropium bromide 0.5 mg in 3 mL.

- **MDI versus nebulizer** – 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 $PaCO_2$ [28,31].

- **Efficacy** – 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. Studies comparing SABAs with SAMAs are limited, but do not demonstrate a clear benefit to either medication [17]. Combination therapy with albuterol and ipratropium is clearly superior to albuterol alone in stable COPD, but studies in acute exacerbations are limited [15,17]. Nonetheless, it is common practice to use the combination for COPD exacerbations.

Subcutaneous injection of SABAs (eg, terbutaline, epinephrine) carries a high risk for inotropic and chronotropic adverse effects, such as arrhythmias or myocardial ischemia, and is virtually never used for COPD exacerbations.

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].

Muscarinic antagonists — We suggest use of the combination of a 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 [1,17,33]. (See 'Muscarinic antagonists' above.)

- **Dose and administration** – 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. Alternatively, a combination ipratropium-albuterol soft mist inhaler (SMI) can be used, 1 inhalation, approximately every hour for two to three doses and then every two to four hours as needed, guided by the response to therapy [34]. Ipratropium is also available in an MDI that can be used with a spacer, 2 to 4 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".)

- **Efficacy** – A systematic review identified a small number of trials that compared a combination of SAMA (ipratropium, glycopyrrolate) plus SABA (albuterol, metaproterenol, fenoterol) with SABA alone and did not find an added benefit to the combination when assessed at 90 minutes [17]. However, in stable COPD, the combination of SAMA plus SABA provides superior bronchodilation compared with SABA alone. Thus, this combination is often used to treat COPD exacerbations.

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 [35]. 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) [36], which is similar to or better than the effect seen in severe asthma exacerbations [37]. (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].

Systemic glucocorticoids — 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 [12,38,39]. 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 [38]. 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 [1,12]. 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 3) [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 [20,39,40]. 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 [40]. 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 [41]. 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 [1,12,42-44]. 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 [12]. 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 [45]. 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 [20]. 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) [42]. 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 "Management of refractory chronic obstructive pulmonary disease", section on 'Systemic glucocorticoids' and "Glucocorticoid withdrawal", section on 'Recommended tapering regimen'.)

- **Efficacy** – Systemic glucocorticoids, when added to the bronchodilator therapies described above, improve symptoms and lung function, and decrease the length of hospital stay [1,20,38,45,46]. 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) [38]. 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 [47]. 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 side 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 [1,12,48]. 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.

Potential treatments for hospitalized patients with SARS-coronavirus-2 infection (COVID-19) are discussed separately. (See 'Advice related to COVID-19' above and "COVID-19: Management in hospitalized adults" and "COVID-19: Management of the intubated adult".)

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 [49].

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 [50-52]. 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 [52]. 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 [53]. 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 [36].

- 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 [1,50,51].

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 5^{th} to 6^{th} 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 10^{th} to 12^{th} 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 chronic obstructive pulmonary disease (COPD) (The Basics)")

- Beyond the Basics topics (see "Patient education: Chronic obstructive pulmonary disease (COPD) treatments (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Triage** – An exacerbation of COPD is characterized by an acute increase in symptoms (ie, cough, sputum production, dyspnea) beyond normal day-to-day variation that leads to a change in medication. An approach to determining whether a patient needs hospitalization or can be safely managed at home is provided in the algorithm (algorithm 1). (See 'Introduction' above and 'Triage to home or hospital' above.)

- **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.)

- **Titrating supplemental oxygen** – Patients with hypoxemia due to an exacerbation of COPD should receive supplemental oxygen. 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**). (See 'Oxygen therapy' above.)

- **Ventilatory support** – Noninvasive ventilation (NIV) improves numerous clinical outcomes and is the preferred method of ventilatory support in many patients with an acute exacerbation of COPD. Invasive mechanical ventilation is required in patients with respiratory failure who fail NIV, do not tolerate NIV, or who have contraindications to NIV. Both NIV and invasive mechanical ventilation for patients with an exacerbation of COPD are discussed separately. (See 'Ventilatory support' above and "Noninvasive ventilation in adults with acute respiratory failure: Benefits and contraindications" and "Invasive mechanical ventilation in acute respiratory failure complicating chronic obstructive pulmonary disease".)

- **Short-acting bronchodilators** – We recommend that all patients having a COPD exacerbation receive inhaled short-acting bronchodilator therapy (**Grade 1B**). Short-acting beta adrenergic agonists (SABA; eg, albuterol, levalbuterol) have a more rapid onset of action than the short-acting muscarinic antagonist (SAMA) ipratropium, so a SAMA-SABA combination (our choice) or SABA alone is preferred over monotherapy with ipratropium (table 4). (See 'Beta adrenergic agonists' above and 'Muscarinic antagonists' above.)

  - The usual dose for relief of acute symptoms is two inhalations every hour for two to three doses and then every two to four hours based on the patient's response. (See

'Beta adrenergic agonists' above.)

- Typical doses of albuterol in this emergency department or hospital are one to two inhalations (most commonly two, occasionally four; 90 mcg per inhalation) by MDI with a spacer or 2.5 mg (diluted to a total of 3 mL with sterile normal saline) by nebulizer every hour for two to three doses and then every two to four hours as needed. (See 'Beta adrenergic agonists' above.)

- When given by nebulization, ipratropium 0.5 mg (500 mcg) is mixed with albuterol 2.5 mg in 3 mL and administered every hour for two or three doses and then every two to four hours as needed. Alternatively, a combination ipratropium-albuterol soft mist inhaler (SMI) can be used, one inhalation, approximately every hour for two to three doses and then every two to four hours as needed. (See 'Muscarinic antagonists' above.)

- For patients 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 the majority of 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 'Oral glucocorticoid therapy' above and 'Systemic glucocorticoids' 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 (eg, oral oseltamivir or an intravenous agent) may be appropriate for exacerbations triggered by influenza virus, depending on timing and susceptibility patterns. The use of COVID-19-specific therapies (eg, monoclonal antibodies, JAK inhibitors, anti-interleukin-6 agents, remdesivir) for patients with COVID-19 is discussed separately. (See 'Antimicrobial therapy' above and 'Antiviral and antimicrobial agents' above and "Management of infection in exacerbations of chronic obstructive pulmonary disease", section on 'Summary and recommendations' and "COVID-19: Management in hospitalized adults" and "COVID-19: Management of adults with acute illness in the outpatient setting".)

- **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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