Management of Acute Exacerbation of Asthma and Chronic Obstructive Pulmonary Disease in the Emergency Department

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KEYWORDS

• Asthma • Asthmatic crisis • COPD • AECOPD

KEY POINTS

- Management of severe asthma and chronic obstructive pulmonary disease (COPD) exacerbations require similar medical interventions in the acute care setting.
- Capnography, electrocardiography, chest x-ray, and ultrasonography are important diagnostic tools in patients with undifferentiated shortness of breath.
- Bronchodilators and corticosteroids are first-line therapies for both asthma and COPD exacerbations.
- Noninvasive ventilation, magnesium, and ketamine should be considered in patients with severe symptoms and in those not responding to first-line therapy.
- A detailed plan reviewed with the patient before discharge can decrease the number of future exacerbations.

INTRODUCTION

Acute asthma and chronic obstructive pulmonary disease (COPD) exacerbations are the most common respiratory diseases requiring emergent medical evaluation and treatment. Asthma accounts for more than 2 million visits to emergency departments (EDs), and approximately 4000 annual deaths in the United States.[1] In a similar fashion, COPD is a major cause of morbidity and mortality. It affects more than 14.2 million Americans (±9.8 million who may be undiagnosed).[2] COPD accounts for more than 1.5 million yearly ED visits and is the fourth leading cause of death

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worldwide.[3,4] Both asthma and COPD exacerbations impose an enormous economic burden on the US health care budget with estimates of more than $56 billion annually for asthma,[5] and $49.9 billion annually for COPD.[4] A recent study found that, despite significant efforts to educate the public and increase disease awareness, the rates of COPD hospitalizations have increased by 20% to 30% between 2002 and 2012. The inpatient monetary charges for these hospitalizations have increased by an alarming 125%, and the rate of hospital readmissions for patients with poorly controlled COPD remains at 21%.[6]

Asthma and COPD are chronic, debilitating disease processes that have been differentiated traditionally by the presence or absence of reversible airflow obstruction. In daily clinical practice, it is difficult to differentiate these 2 obstructive processes based on their symptoms, and on their nearly identical acute treatment strategies. Their major differences are important only when discussing anatomic sites involved, long-term prognosis, and the nature of inflammatory markers. These aspects affect disease response to certain pharmacologic treatment options.[7]

DEFINITIONS

The Global Initiative for Asthma (GINA) described asthma as an allergic disease, typically commencing in childhood,[2,8] and characterized by increased bronchial hyperresponsiveness, increased vascular permeability, bronchial smooth muscle spasm, and the release of inflammatory mediators. This pathophysiology translates into recurrent episodes of wheezing, difficulty breathing, chest tightness, and coughing.[9]

Asthma exacerbations are variable and episodic. Asthma can be triggered by a plethora of environmental agents, infectious precipitants, emotional or exercise states, and diverse exposure to ingested or inhaled agents, typically resolving completely either spontaneously or with treatment.[8,10]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define COPD as an acquired and preventable disease resulting primarily from tobacco smoking, and characterized by persistent airflow obstruction, and decline in progressive lung function.[2,4] It usually develops after the fourth decade of life, and it is characterized by shortness of breath, cough, and sputum production.[4] The airflow limitations are classically progressive and associated with an abnormal inflammatory response to diverse inhaled agents, gases, and particles.[7]

PATHOPHYSIOLOGY

There is not strong evidence suggesting histopathologic overlap between these 2 obstructive entities, known as the asthma–COPD overlap syndrome.[2] The most important pathologic difference between asthma and COPD is the inflammatory cells that mediate each respective disease process. Eosinophils and CD4 cells mainly mediate asthma, whereas neutrophils and CD8 cells mediate COPD.[2] This basic difference allows inhaled corticosteroids (CS) to be more efficacious against eosinophilic-mediated asthma, and largely ineffective against the primarily neutrophilic inflammation seen in COPD.[2,7] Regardless of their pathologic differences or their similar inciting agents, it is paramount that emergent risk stratification and treatment modalities be initiated expeditiously to decrease clinical deterioration, morbidity, and mortality.

RISK STRATIFICATION

Risk stratification of the severely short of breath (SOB) patient requires several steps and can be a difficult feat when an undifferentiated patient with SOB presents to the

ED. The practitioner should undertake a methodologic approach to optimize the acquisition of a pertinent history and quickly determine the best management pathway. **Box 1** provides some high-yield questions that will aid in the initial assessment of the dyspneic patient.[4,11]

After these initial questions, the severity of the exacerbation can be assessed with objective physical findings such as vital signs, including oxygen saturation, heart rate (HR), and respiratory rate; degree of wheezing and air movement; use of accessory muscles; degree of difficulty with speech; peak expiratory flow; and end-tidal carbon dioxide ($ETCO_2$) monitoring.[4,11] It is imperative to understand that the absence of severity markers does not exclude the presence of a life-threatening disease process. A helpful algorithm to aid in differentiating between mild, moderate, and severe exacerbation is presented in **Fig. 1**.

The final step during the primary assessment of the patient with SOB is the essential consideration that wheezing and respiratory distress can also be found in multiple other disease states. An adequate differential diagnosis must be formulated to prevent the creation of an anchoring bias, which would prevent a clinician from maintaining a broad differential diagnosis. **Box 2** illustrates a differential diagnosis of wheezing in adults and children.

ACUTE DECOMPENSATED HEART FAILURE

The acutely undifferentiated patient with SOB may have multiple comorbidities that might contribute or disguise the exact inciting disease process. Two commonly encountered examples are heart failure (HF) and COPD. These 2 entities are frequently encountered in the elderly and tobacco smoker. Several studies estimate the prevalence of HF in COPD patients to be somewhere between 20% and 30%.[12] Similar studies have also reported that the presence of HF in COPD is associated with worse clinical outcomes.[13,14]

DIAGNOSIS

Spirometry

GOLD, GINA, and other evidenced-based guidelines have been developed as blueprints for the identification, prevention, and treatment of both these obstructive

Box 1
Important risk factors in the asthmatic/COPD patient

- Previous endotracheal intubations
- Previous intensive care unit admissions
- ≥2 non-ICU hospitalizations in the past 1 year
- ≥3 ED visits in the past month
- Chronic use of oral corticosteroids
- Medication noncompliance
- Living in poverty with no access to health care
- Using ≥2 SABA pressurized metered dose inhalers monthly

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; SABA, short-acting β-agonist.

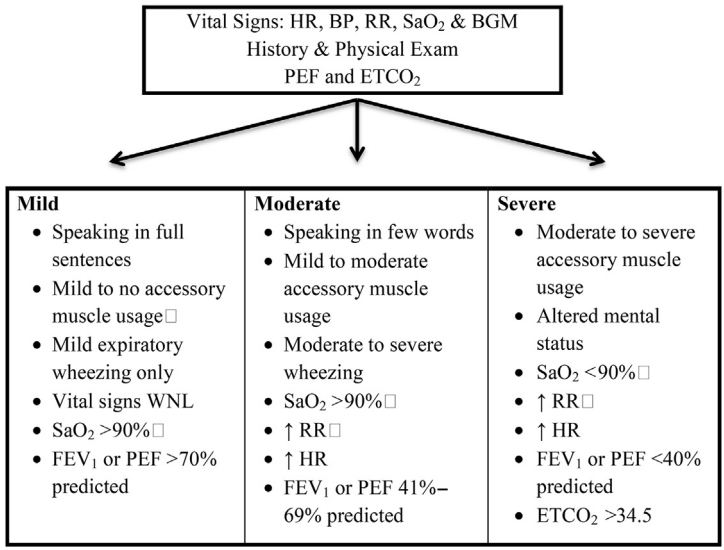

Fig. 1. Dyspneic exacerbation severity algorithm. BGM, blood glucose monitor; BP, blood pressure; $ETCO_2$, end-tidal carbon dioxide; FEV_1, forced expiratory volume in 1 second; HR, heart rate; PEF, peak expiratory flow; RR, respiratory rate; WNL, within normal limits.

entities. Both GOLD and GINA recommend baseline spirometry to diagnose and classify these diseases.[4,8] Despite this standard recommendation, there is no clinical benefit to performing spirometry in the acute care setting. Spirometry is not a suitable tool for the emergent management of the undifferentiated dyspneic patient.

Box 2
Differential diagnosis of wheezing

Adults	Children
• Upper respiratory tract infection	• Upper respiratory tract infection
• Pneumonia	• Croup
• Asthma	• Tracheomalasia
• Chronic obstructive pulmonary disease	• Bronchiolitis
• Congestive heart failure	• Asthma
• Chronic bronchitis	• Pneumonia
• Gastroesophageal reflux disease	• Foreign body
• Acute coronary syndrome	
• Pulmonary embolism	
• Foreign body	
• Pneumothorax	
• Cystic fibrosis	
• Vocal cord dysfunction	

Laboratory Tests

There is currently no laboratory test that will specifically identify asthma or acute exacerbations of COPD (AECOPD) as the etiology of the acutely patient with SOB. Any standard serum laboratory studies should only be drawn to assist in deciphering the etiology of the acute decompensation. Sputum testing is unreliable and should not be gathered, unless tuberculosis is suspected as the underlying etiology of the exacerbation. GOLD only recommends sputum testing in the AECOPD patient who has failed initial antibiotic therapy.[4] Viruses are strongly associated with AECOPD; therefore, testing for influenza may provide important implications in management of these patients.[15]

Blood Gas Analysis

Arterial blood gas analysis is a routine test performed in the severe asthmatic and AECOPD patient. Several guidelines recommend its use in moderate and severe respiratory exacerbations: when the pulse oxygen saturation (SaO_2) is less than 92% on room air; and to follow pH, partial pressure of carbon dioxide (P_{CO_2}), and partial pressure of oxygen. One must question the benefit of an arterial over a venous blood gas given the pain severity, the possibility of aneurysmal formation, arterial laceration, infection, and infrequently, the loss of limb.[16–26] These possible risks of the procedure must be coupled with the understanding that a normal P_{CO_2} in a venous blood gas analysis excludes arterial hypercarbia, making this painful and possibly complicated procedure unnecessary.[16–26]

Capnography

$ETCO_2$ during an AECOPD may be useful in the risk stratification of these patients. Doğan and colleagues[27] found that, when measuring with mainstream capnography devices, $ETCO_2$ levels were higher in admitted patients than those who were discharged from the ED. These levels must be obtained before any bronchodilator treatment. After the first bronchodilator treatment was completed, the $ETCO_2$ between the 2 groups showed no difference. This study also showed a strong correlation between $ETCO_2$ and arterial P_{CO_2}, previously demonstrated by Cinar and colleagues.[28]

Electrocardiogram

Electrocardiography is an essential component in the acute evaluation of the patient with SOB. Part of the reported 58% increased mortality of patients with COPD between 1990 and 2010 has been linked to adverse cardiovascular events.[29] Although the exact pathophysiologic link remains unclear, data suggest that this could be caused partly by cardiac dysrhythmias.[30,31] **Fig. 2** demonstrates commonly encountered ECG changes that may be found in the AECOPD. These changes can be attributed to the clockwise rotation of the heart and the right atrial and ventricular hypertrophy that is seen in the COPD patient. Furthermore, P-wave verticalization is likely caused by the downward displacement of the heart owing to the progressive flattening of the diaphragms. This pathology is owing to the right atrium being physically anchored to the diaphragm by a strong aponeurosis.[32]

Other ECG findings in COPD include:

- S waves in leads I, II, and III;
- R/S ratio less than 1 in leads V5 or V6; and
- The lead I sign—isoelectric P wave, QRS amplitude less than 1.5 mm, and T wave amplitude less than 0.5 mm in lead I.

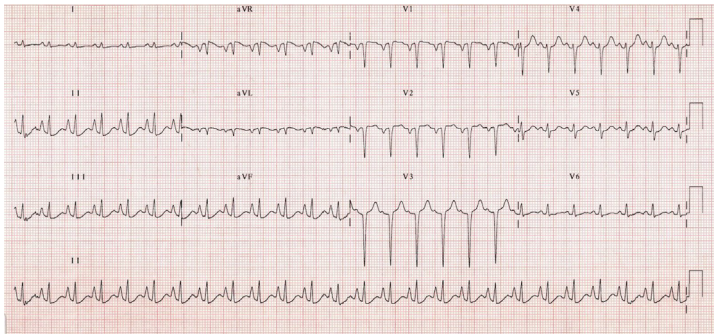

Fig. 2. (1) Tachycardia. Multifocal atrial tachycardia is rare, but specific to chronic obstructive pulmonary disease (COPD).[33] (2) Right axis deviation. (3) P wave axis of greater than 60° (considered to be 96% sensitive for COPD.[34]) (4) Low-voltage QRS amplitude in I, aVL, V5-V6. (May be found in leads II, III, or aVF [<5 mm]). (5) P pulmonale (peaked P waves in leads II, III, or aVF [>2.5 mm]). (*From* Burns E. The ECG in chronic obstructive pulmonary disease. Life in the Fast Lane. 2012. Available at: http://lifeinthefastlane.com/ecg-library/copd/. Accessed May 29, 2015. Life in the Fast Lane is licensed under a Creative Commons ShareAlike 4.0 International User's License http://creativecommons.org/licenses/by-sa/4.0/.)

If these criteria seem overly complex, a more simplified diagnostic marker is finding a P wave in lead aVL, or the P wave amplitude in lead III greater than in lead I.[35]

Radiography

The posteroanterior and lateral chest radiograph is the most widely used imaging modality in the evaluation of the acutely dyspneic patient. Typical findings include a flattened diaphragm, an increased anteroposterior diameter, an enlarged retrosternal airspace, a narrow vertical cardiac silhouette, and bullae.[36] Although none of these findings is diagnostic, a chest x-ray is more importantly obtained to rule out other causes of shortness of breath, such as pneumothorax, pulmonary infiltrates, or pulmonary edema. Tsai and colleagues[37] found that 21% of patients had their management altered by an initial chest x-ray. Pulmonary embolism has been found in 3% of COPD patients presenting to the ED.[38]

Chest radiography should be considered routine in the patient with an AECOPD. In patients with established asthma, there is more room for clinical judgment, and practitioners should consider a chest x-ray in patients who (1) are in extremis, (2) have clinical markers of pneumonia or pneumothorax, (3) are not responding to conventional therapy, (4) are presenting with new onset wheezing, and presumed de novo asthma, and (5) are at risk for an alternative diagnosis, for example, HF in the older adult and foreign body aspiration in the young child with wheezing.

Ultrasonography

Cardiopulmonary ultrasonography has become an important diagnostic tool in the ED setting because it decreases exposure to radiation. Three main protocols have come into favor. These include Lung Ultrasound in the Critically Ill (LUCI), Bedside Lung Ultrasonography in Emergency (BLUE), and Fluid Administration Limited by Lung Sonography (FULL).[39] Gallard and colleagues[40] found that ultrasonography has an accuracy of 95% in diagnosing COPD or asthma exacerbations. This reinforced the findings of Silva and colleagues,[41] who found a 92% accuracy of ultrasonography in diagnosing these conditions.

TREATMENT

Oxygen

Oxygen therapy is a key feature in the management of an undifferentiated patient with SOB. In an acute asthma exacerbation, GINA and the British Thoracic Society recommend that oxygen be the first-line treatment. They strongly emphasize this recommendation with the understanding that hypoxia must be addressed expeditiously and oxygen administration should be monitored closely for efficacy. This differs significantly from their guidelines for the AECOPD patient. The Fio_2 provided to this patient population should be no greater than 28%. Bronchodilators are to be given with compressed air rather than oxygen. These recommendations stem from the knowledge that hyperoxia leads to decreased minute ventilation and hypercapnia.[42] Such increases in carbon dioxide are more likely to be seen in older patients and those with a home oxygen dependence, and can cause neurologic and cardiac depression.[43]

Austin and colleagues[44] showed a reduced mortality in COPD patients with titrated oxygen therapy. Oxygen administration guidelines should therefore be in place in both the prehospital setting as well as in the ED. Oxygen can be titrated according to a saturation of peripheral oxygen (SpO_2), with no oxygen given at an SpO_2 of greater than 92%, 2 to 3 L via nasal cannula at an SpO_2 of 85% to 92%, and a face mask with higher flows used for an SpO_2 of less than 85%.[45] An arterial blood gas can then be obtained to further guide oxygen requirements.

Bronchodilators

The first-line pharmacotherapy in the emergent management of the asthmatic crisis and AECOPD is the administration of bronchodilators.[46] These agents target the bronchial hyperactivity and attempt to reverse, or ameliorate airflow obstruction. Although COPD is usually considered an irreversible process, most acute COPD exacerbations have a reversible component that must be targeted. The primary pharmacotherapy agents used are short-acting β2-agonists (SABA) and ipratropium bromide.

Short-acting β_2-receptor agonists

SABA relax pulmonary smooth muscle by stimulating airway β_2-adrenergic receptors, increasing intracellular cyclic adenosine monophosphate. This increase in cyclic adenosine monophosphate inhibits smooth muscle bronchoconstriction. SABA's typical time of onset is seconds to minutes, with peak effect at 30 minutes and a half-life of 4 to 6 hours.[4,8] The most widely used SABA is albuterol, a racemic mixture of 2 enantiomers, namely (R)-albuterol and (S)-albuterol. (R)-albuterol is the active form, binding to β2-receptors and provides the desired bronchodilation. This also causes the more undesired, tachycardia, tremors, and anxiety/restlessness. (S)-albuterol, the inert form, is hypothesized to possibly have detrimental effects on airway function.[46] This was the premise of the development of levalbuterol, a purified version of the (R)-albuterol enantiomer that was marketed as having fewer of the unwanted cardiac adverse effects than racemic albuterol. Multiple studies have shown that continuous nebulized levalbuterol is not superior to continuous nebulized albuterol and that levalbuterol had no beneficial effects on HR.[47,48] In a metaanalysis of 7 clinical trials conducted by Jat and Khairwa,[49] there was no evidence supporting the theory that levalbuterol is superior to albuterol regarding efficacy and patient safety.

Long-acting β_2-receptor agonists

Long-acting β_2-receptor agonists (LABAs) such as salmeterol and formoterol were widely used in the early 1990s because they provided approximately 12 hours of bronchodilation. In 1993, Castle and colleagues[50] showed significant evidence that

salmeterol had a 3-fold mortality increase in asthmatic patients. This finding was quickly confirmed in 1996 by the US Food and Dug Administration's Salmeterol Multicentre Asthma Research Trial (SMART). The study had to be prematurely stopped owing to increased exacerbations and mortality.[51] An additional study performed by Mann and colleagues[52] also demonstrated increased asthma exacerbations.

This is in contrast with current recommendations provided by the American College of Chest Physicians and the Canadian Thoracic Society to prevent AECOPD. LABAs have been shown to improve quality of life and lung function while decreasing moderate and severe exacerbations in COPD patients. Rate of adverse events and mortality were not increased compared with placebo in this patient population.[53] A LABA combined with an inhaled CS is preferable to monotherapy with either agent.

Anticholinergics

Inhaled ipratropium bromide (Atrovent) elicits its bronchodilatory effect by competitively inhibiting the muscarinic acetylcholine receptors of the pulmonary smooth muscle. Its time of onset is approximately 15 minutes, with a peak effect at 60 to 90 minutes and half-life of 6 to 8 hours, making it slower in onset and longer in duration than SABA.[54] This explains the common practice of using these inhaled agents in combination. The GOLD guidelines recommend a SABA as a first-line agent owing to its faster onset of action, followed by anticholinergics if a prompt response is not attained clinically.[4] The authors of this article agree with the findings of Vézina and colleagues,[55] who found that combined pharmacotherapy is more effective in decreasing ED admissions with no evidence of adverse effects. Ipratropium bromide can also be considered as a good alternative in patients who are intolerant of SABA side effects. The agent has been linked to lower ED admission rates in acutely severe exacerbations and may decrease the overall ED duration of stay.[56–58] A similar, but longer-acting antimuscarinic, tiotropium, has been shown to be an effective maintenance bronchodilator in both COPD and asthma patients. Kerstjens and associates[59] demonstrated that tiotropium improved symptomatic control in patients with poorly controlled symptoms who were on inhaled CS and LABAs and reduced severe exacerbations by 21%. In the first 24 hours of the respiratory obstructive crisis, some believe that the adrenergic receptors, which constitute the majority of pulmonary airway receptors, are downregulated and perhaps temporarily unresponsive to β_2-receptor agonists. During this time, pulmonary muscarinic acetylcholine receptors remain functional leading to their contribution in bronchodilation.[60–62]

Delivery mode

Method of pharmacotherapy delivery is via a pressurized metered dose inhaler with a holding chamber or an oxygen-driven nebulizer. The current literature does not show any difference in outcomes based on route of administration, except for slightly shorter ED duration of stay in those treated with gas-driven nebulizers.[63,64]

Magnesium sulfate

Intravenous (IV) magnesium sulfate ($MgSO_4$) is suggested to produce pulmonary smooth muscle relaxation via calcium receptor blockade or by activation of adenyl cyclase at the smooth muscle cellular level.[65] Regardless of its mechanism of action, its efficacy on the acute asthmatic crisis or the AECOPD remains uncertain, despite guidelines like GINA and GOLD advocating its use.[4,8] Two studies were recently undertaken to ascertain this agent's efficacy. The first, conducted by Goodacre and colleagues,[66] failed to show that either IV or nebulized $MgSO_4$ provided any clinically relevant benefit in adults with severe acute asthma. On the contrary, a second study performed by Kew and colleagues[67] found that IV $MgSO_4$ reduced hospital

admissions and improved lung function when other pharmacotherapy had failed to ameliorate the acute exacerbation.

Corticosteroids

CS treatment is also considered first-line in the emergent management of the asthmatic crisis and AECOPD. CS have a complex mechanism of action that ultimately leads to the inhibition of potent inflammatory mediators and the reduction of airway inflammation. A recent Cochrane review conducted by Walters and colleagues[68] demonstrated that the use of CS was associated with a greater than 50% reduction in treatment failure. The number of patients needed to treat with CS to prevent 1 treatment failure was 9. This same study also showed that CS provided a 30-day relapse rate reduction, and a shorter hospital duration of stay, despite no association with decreased mortality.[68] The choice of which systemic CS (SCS) to use has been debated, and common practice dictates the use of glucocorticoids (prednisone, prednisolone, or methylprednisolone), because they are the most widely studied making them the preferred choice over SCS with mineralocorticoid effects like hydrocortisone.[69] There is still ongoing research regarding the most appropriate dose, route of administration, and duration of therapy. Currently, there is good consensus that there is no inferiority between oral and parenteral treatment with regards to rates of treatment failure, relapse rate, and mortality.[68,70] Therefore, if the patient can tolerate an oral agent, provide therapy orally and reserve parenteral treatment for those patients who cannot tolerate oral treatment.

Of note, a new pilot study conducted by Mendes and colleagues[71] regarding the emerging use of inhaled CS showed that, in adults with airflow obstruction, a single standard dose of an inhaled CS provided simultaneously with inhaled albuterol acutely potentiated the effects of the albuterol-induced pulmonary smooth muscle relaxation and increased the forced expiratory volume in 1 second (FEV_1) response versus the standard method.

Initial CS dosages have also been a topic of great debate secondary to the misconception that severity of disease warrants higher dosages of treatment. In 2013, Cheng and colleagues[72] performed a metaanalysis of 12 studies totaling 1172 patients; they were not able to demonstrate any benefit to CS dosages of greater than 80 mg/d. These findings were consistent with Alia and colleagues's[73] study from 2011, which demonstrated that SCS dosages of 0.5 mg/kg every 6 hours were sufficient, and higher dosages were unwarranted for achieving clinical outcomes. For example, higher dosages did not have decreased duration of stay, decreased length of ventilation, or decreased treatment failure with noninvasive ventilation (NIV). Despite no benefit found in larger dosages of SCS therapy, Schacke and colleagues[74,75] have shown that the risk of adverse effects increases with increased doses of CS. The main adverse reactions with larger doses of CS were hyperglycemia, myopathies, neurologic effects like anxiety and delirium, increased rate of infection, hypertension, and gastrointestinal bleeding.[74,75] These adverse effects were also documented by Kiser and colleagues,[76] who found the association of increased rates of hyperglycemia, need for insulin therapy, and increased rates of invasive fungal infections in patients that were given CS doses of greater than 240 mg/d. Dosages of greater than 2 mg/kg per day do not provide any clinical benefit, and will likely provide greater side effects in the management of the critically ill asthmatics or AECOPD.

The last vastly debated concept in CS treatment is the duration of treatment therapy. The literature has described a wide range of therapy from 5 days to 8 weeks. The Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) trial conducted by Leuppi and colleagues[77] demonstrated that short-term therapy was

noninferior to a longer duration. It showed no difference in mortality, rate of relapse, or change in recovery of lung function based on treatment duration.[77]

Upon completion of these initial interventions, any additional treatment is based on the patient's clinical status. **Fig. 3** provides a suggested treatment algorithm for patients with severe asthma.[78] It can also serve as a helpful algorithm in the treatment of AECOPD.

Antibiotics

Antimicrobial pharmacotherapy is perhaps the only emergent treatment recommendation that will differ between the asthmatic and the AECOPD. As opposed to an asthmatic event, it is estimated that approximately 8 of every 10 AECOPD episodes precipitated by a pulmonary infection, with either a bacterial, viral, or fungal pathogen.[79–81] Furthermore, these authors estimate that 50% of the microbial-induced exacerbations are attributed to a bacterial pathogen, warranting antibiotic therapy. White and colleagues[82] have also suggested that antibiotic therapy in an AECOPD will decrease the risk of progression to pneumonia and will catalyze bacterial eradication that in turn will improve airway inflammation in the acute exacerbation. Macrolides are the best class of antibiotics class for the treatment of AECOPD. Martinez and colleagues[83] determined that macrolides have added antiinflammatory and immunomodulatory effects, in addition to their antibacterial efficacy. Barnes[84] has postulated that macrolide therapy may increase the pulmonary smooth muscle's response to CS via the increased recruitment of the enzyme histone deacetylase 2 that is integral in the inflammatory response seen in COPD patients. Finally, although macrolides may have additional benefits over other classes of antibiotics, if an allergic reaction develops, other commonly used agents such as β-lactams and fluoroquinolones are deemed appropriate alternatives.[84]

Noninvasive Ventilation

The airway management of a decompensating asthmatic and COPD patient must be monitored meticulously and prompt changes must be made if first-line therapy is not ameliorating the respiratory crisis. The early recognition and appropriate modification in management may prevent further decompensation and increased mortality. Carson and colleagues[85] report that patients who are decompensating warrant NIV. NIV is the mainstay of therapy in the acute management of most reversible respiratory emergencies. This treatment modality is best provided via full facial mask, although other delivery methods are available. It is postulated that NIV is a direct bronchodilator.[86] NIV also recruits alveoli secondary to external positive end expiratory pressure (PEEP), offsetting intrinsic PEEP.[87] Alveolar recruitment improves ventilation–perfusion mismatch by preventing airway closure and reducing the work of breathing.[88] NIV can be used for short periods of time as deemed clinically necessary and carries a lower risk of nosocomial pneumonia than endotracheal intubation (ETI).[89] **Fig. 3** suggests starting inspiratory positive airway pressure and expiratory positive airway pressure at 8 cm H_2O and 3 cm H_2O, respectively. The authors of this article strongly encourage that the practitioner remain at the patient's bedside directly monitoring work of breathing and serially increasing both inspiratory positive airway pressure and expiratory positive airway pressure to higher pressures within a 30 minute trial to optimize nebulizer and overall treatment time. A recent Cochrane review indicated that patients with acute asthma exacerbation who were treated with NIV had decreased admission rates, decreased duration of ICU stay, and an overall shorter hospital stay, although there was no clear benefit for reduced ETI or mortality.[90] Last, NIV has been shown to be safe in pregnant patients and in pediatric populations.[85] Relative contraindications include facial or

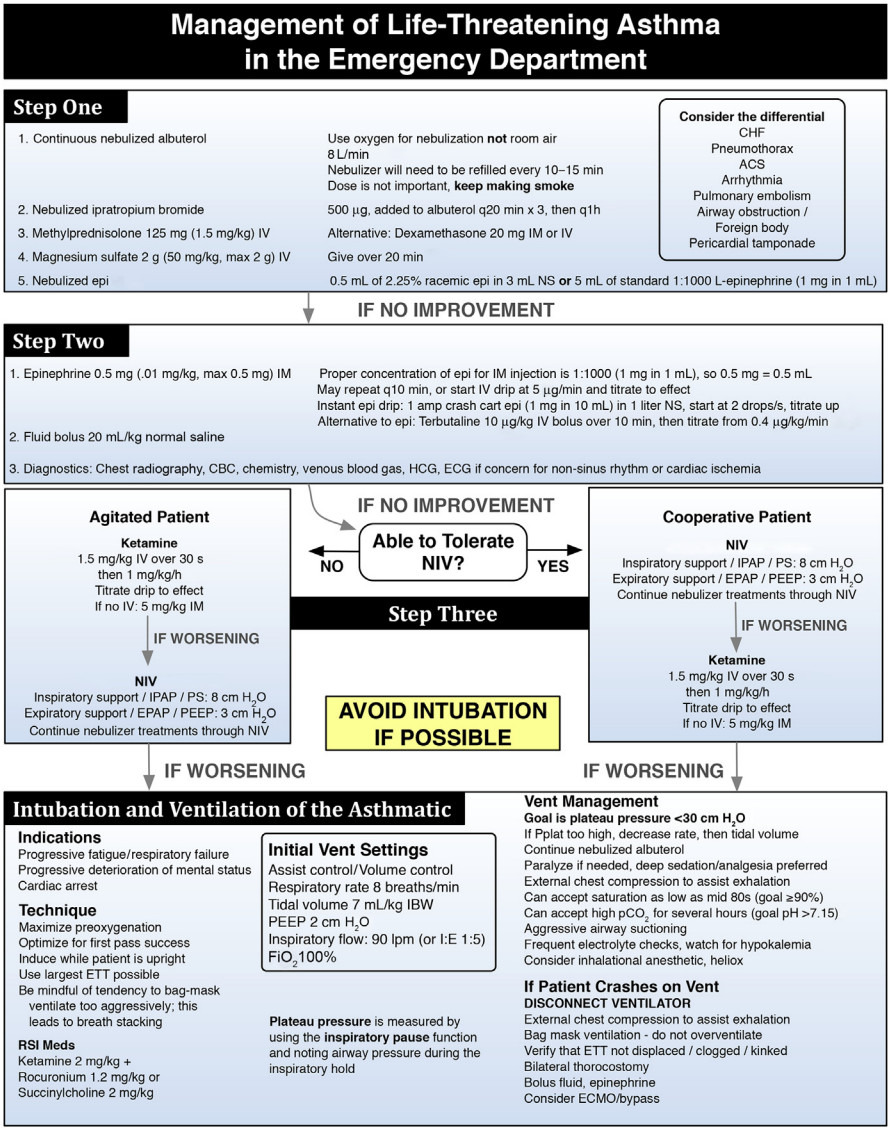

Fig. 3. Suggested treatment algorithm for patients with severe asthma. ACS, acute coronary syndrome; CBC, complete blood count; CHF, congestive heart failure; ECG, electrocardiograph; ECMO, extracorporeal membrane oxygenation; EPAP, expiratory positive airway pressure; ETT, endotracheal tube; epi, epinephrine; FiO_2, fraction of inspired oxygen; IBW, ideal body weight; IM, intramuscular; IPAP, inspiratory positive airway pressure; IV, intravenous; NIV, noninvasive monitoring; NS, normal saline; pCO_2, partial pressure of carbon dioxide; PEEP, positive end expiratory pressure; Pplat, airway plateau pressure; PS, pressure support. (*Courtesy of* RJ Strayer, P Andrus, R. Arntfield and emupdates.com; used with permission.)

esophageal trauma or surgery, deformities of the upper airway, copious secretions, or an uncooperative patient. Absolute contraindications are cardiac or respiratory arrest.[91]

High-Flow Nasal Cannula Oxygen Therapy

High-flow nasal cannula oxygen therapy provides heated and humidified oxygen through a nasal cannula at a flow rate of up to 60 L/min. It can be used as an alternative to NIV in patients who have poor tolerance to facial masks, and is helpful in asthmatics and COPD patients because it decreases anatomic dead space.[92] Although it cannot actively enhance tidal volume, the high flow increases airway pressure and decreases some the resistance of expiratory flow. The end-expiratory lung volume is also increased with an effect more pronounced in patients with a high body mass index.[93] High-flow nasal cannula oxygen therapy has also been found to provide better thoracoabdominal synchrony than with a facemask NIV. Unlike with a conventional nasal cannula, at high flows the actual inspiratory fraction of oxygen (Fio_2) delivered by the high-flow nasal cannula better approximates the predicted Fio_2.

Heliox

Heliox is a compound mixture of 80% helium and 20% oxygen. It can also be considered as an adjuvant in the early management of asthma before oxygen saturation requirements become the deciding parameter. Helium is a chemically inert, odorless, tasteless, noncombustible gas that has a lower molecular density than oxygen and air.[94] This lower density can serve as a better transport modality than traditional room air or 100% oxygen-driven nebulizers for the penetration of bronchodilating, anticholinergic, and antiinflammatory agents. It has been shown that heliox-driven bronchodilation brings about more rapid and greater improvement in FEV_1, forced vital capacity, and maximal expiratory flow rate than the traditional nebulizer methods.[95] Therefore, in asthmatic and AECOPD patients with an FEV_1 of 50% or less, heliox-driven nebulization treatments lead to better spirometry measurements than do air-driven nebulization treatments.[94] The most recent metaanalysis performed by Rodrigo and Rodriguez-Castro[96] in 2014 showed that β_2-agonist heliox-driven nebulization lowered the rate of ED admissions from 36% to 25% versus standard oxygen-driven nebulization. This metaanalysis warrants additional prospective testing and comparison between heliox- and oxygen-driven nebulization.

Ketamine

Ketamine is a potent dissociative analgesic that can be used as a rescue agent in patients who have severe asthma and AECOPD that are refractory to first-line treatment options. It is characterized by an onset of action within 60 seconds, peak tissue distribution within 7 to 11 minutes, and an hepatic excretion half-life of 2 to 3 hours.[97] Ketamine holds several properties that can aid the AECOPD and severely asthmatic patient. First, ketamine has been shown to block the activation of *N*-methyl-D-aspartic acid (NMDA) receptors in the lung parenchyma. These NMDA receptors are responsible for stimulating the unwanted pulmonary edema and bronchoconstriction found during an AECOPD and in an asthmatic crisis.[98] Second, in the lung, ketamine has been found to downregulate production of the nitric oxide that is responsible for bronchospasm.[99] Third, ketamine has been found to block the recruitment of macrophages, interfere with cytokine production, and decrease interleukin-4 concentrations. These mechanisms are responsible for unwanted inflammatory changes, airway hyperreactivity, and bronchoconstriction in the acutely severe asthmatic patient.[100] All of these properties, along with the previously discussed upregulation of catecholamine levels and the

anticholinergic effects on bronchial smooth muscle, argue strongly for ketamine as an advantageous adjuvant agent in the management of the AECOPD and decompensating asthmatic. Last, it is important to emphasize that ketamine, like all analgesic, amnestic, anesthetic, and muscle relaxants, be administered in a monitored environment where SaO_2, $ETCO_2$, blood pressure (BP), HR, and appropriate nursing presence is available continuously.

Epinephrine

Perhaps the most underappreciated and underused pharmacotherapy in our armamentarium for the treatment of an asthmatic crisis and the AECOPD is epinephrine. Some iconic practitioners would strongly argue that this agent should be placed on the top of every first-line treatment algorithm published by medical societies, a sentiment that both authors of this article share. The concern for a possible adverse cardiovascular event, increased risk of hypertension in an already uncontrolled hypertensive patient and the possible risk of aggravating the tachycardic state in an already tachycardic patient has placed this previously first-line agent at the bottom, if not completely off treatment algorithms. In 1988, Cydulka and colleagues[101] stated that, despite concerns of old age, concerns of potential adverse cardiac events, or concerns of increased risk of exacerbating BP and HR, epinephrine, dosed at starting doses of 0.3 mg of 1:1000 solution, did not cause any of these adverse reactions. Epinephrine, like many of the first-line agents today, may cause tremors, anxiety, and nausea, and most patients will tolerate these doses with no contraindications.[101] Even increased BP and tachycardia, which can also be attributed to severe anxiety, hypoxia, hypercapnia, and increased work of breathing, actually declined in the older cohort of patients, and only minimally increased in the younger group. In the younger group, BP and HR normalized when patients attained relief from bronchospasm.[101]

A second study published that same year was a study by Spiteri and colleagues[102] that compared terbutaline with epinephrine for the treatment of acute asthma, and it demonstrated that neither agent produced any significant increases in BP or HR, no treatment-related ECG abnormalities, and no observed adverse cardiovascular effects. Both of these studies showed benefit and no significant harm in the use of epinephrine for the treatment an asthmatic crisis. It is time to revisit this topic in a prospective and randomized manner.

Endotracheal Intubation

The decision to intubate should not be taken lightly as manipulation of the airway in a patient with AECOPD or an asthmatic crisis can cause laryngospasm, worsen bronchospasm, and may even increase morbidity. It is estimated that the mortality rate of ICU patients who are intubated for severe asthma is 10% to 20%.[103] Some studies have advocated that the severe asthmatic and COPD patient can be adequately managed without resorting to ETI.[104,105] Despite attempting to refrain from intubating a decompensating asthmatic, once first- and second-line therapies have failed, the practitioner must seriously consider ETI. The clinical decision regarding when to intubate a decompensating asthmatic patient can be aided by clinical signs such as an SaO_2 of less than 90% with maximal supplemental oxygen, bradypnea leading to hypercapnia and respiratory acidosis, altered level of consciousness, and physical exhaustion.[106] The only absolute indications for intubation are respiratory or cardiac arrest.[107]

The usual method for intubating a patient in AECOPD and asthmatic crisis is maximal preoxygenation followed by rapid sequence induction. Ketamine and propofol are both valid options for induction agents. Ketamine creates a catecholamine

release that causes bronchodilation by relaxing bronchial smooth muscles.[108] Because this release of catecholamines can cause hypertension and arrhythmias, ketamine should be avoided in patients with active dysrhythmias. Propofol also has some bronchodilating effects, and it can cause hypotension. Patient selection for this drug also should be considered carefully.

Succinylcholine and rocuronium bromide are the 2 main choices of muscle relaxant for rapid sequence intubation in the ED. It is essential that their respective benefits and possible side effects be understood before selecting an agent. Traditionally, rocuronium has been considered to have a slower time of onset than succinylcholine. Importantly, onset is slower only if rocuronium is used at lower doses of 0.6 to 0.9 mg/kg IV. If a dose of 1.2 mg/kg IV is used, no difference exists in the time of onset of ideal intubating conditions, although the higher dose will lengthen the duration of paralysis.[109] The duration of paralysis with rocuronium is also dose dependent; time to paralysis recovery is reported to occur as early as 30 minutes with a dose of 0.6 mg/kg IV, and it will be double or even triple after a 1.2 mg/kg dose.[109] **Table 1** provides the common side effects encountered with succinylcholine. The most troubling and rare, side effect of rocuronium is anaphylaxis. Regardless of the agent used for paralysis, understanding respective mechanisms of action and side effects is essential.

In the patient with severe asthma and COPD, ETI and positive-pressure ventilation may cause abrupt increases in intrathoracic pressure that in turn decrease venous return and therefore cardiac output. For this reason, time permitting, it is important to optimize the patient's preload before ETI is attempted. A preintubation fluid bolus (as well as use of the ventilator strategies described elsewhere in this article) may help to prevent or attenuate abrupt decreases in BP immediately after ETI.

Post Endotracheal Intubation Documentation

ED and critical care specialists should be diligent in documenting the intubation procedure. A detailed medical record will greatly aid the clinician who attempts extubation when the pathophysiologic state has been reversed. The physician should always document the Cormack–Lehane grading scale (**Fig. 4**), the laryngoscope blade used, any airway adjuvants used, the number of intubation attempts made, a description of any complications, and any confirmation modalities used in the airway management.

Table 1
Side effects of succinylcholine

Side Effect	Remarks
Bradycardia	Occurs especially in small children after repeat doses.
Hyperkalemia	May increase potassium ~0.4 mmol/L in normal patients, but may lead to life-threatening increases in amyotrophic lateral sclerosis, multiple sclerosis, muscular dystrophies, inherited myopathies, denervating injuries, burns, and crush injuries
Fasciculations	Increase: • Oxygen consumption that may cause myalgia • Intragastric pressure, likely by increasing lower esophageal sphincter tone • Intracranial pressure • Intraocular pressure
Malignant hyperthermia	Rare

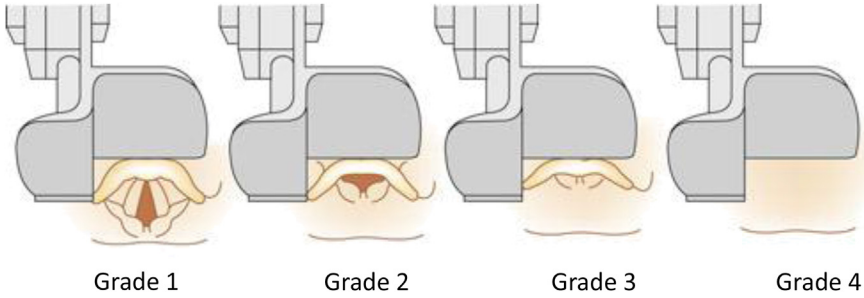

Fig. 4. Cormack–Lehane grading scale. (*From* Bjerkelund CE, Christensen P, Dragsund S, et al. [How to secure free airway?] Tidsskr Nor Laegeforen 2010;130(5):508; with permission.)

Delayed sequence intubation

Delayed sequence intubation (DSI) is an innovative technique used in a subset of the respiratory distress population that optimizes preoxygenation to achieve an oxygenation "safety net" before desaturation. This method allows for appropriate preoxygenation without the risk of gastric insufflation or aspiration.[110] As opposed to the traditional rapid sequence intubation method that consists of providing a sedative and paralytic agent simultaneously with no ventilation until ETI is attained,[111] DSI consists of providing a sedative agent that does not blunt the airway reflexes or spontaneous ventilation before administering the paralytic agent to place the endotracheal tube.[110] As mentioned, ketamine is considered by many as the optimal agent for DSI because it does not blunt patient airway reflexes or spontaneous respirations while providing a dissociative state that allows for the use of NIV,[112] and also providing the much warranted bronchodilation effects.[98–100] A second, and less efficacious agent that could be used, if ketamine's sympathomimetic effects are a concern, is dexmedetomidine, an α-2 agonist that provides sedation with no blunting of airway reflexes or respiratory drive.[113] Dexmedetomidine should not increase the patient's BP or HR; in fact, it can cause significant bradycardia. The typical initial bolus of this agent is 1 μg/kg over 10 minutes, and if needed, an infusion of 0.5 μg/kg per hour can be continued.[114,115] The final possible advantage that has been seen since the advent of DSI is that after the sedative agent and adequate NIV is provided to patients in respiratory failure, the respiratory state may improve in such a dramatic manner, that ETI may be avoided completely.[110] It is critical for providers to have adequate monitoring, time at the bedside, and ancillary support when attempting DSI.

Mechanical Ventilation

Once ETI is achieved, secured, and confirmed, the initial ventilator settings should be optimized to prevent hyperinflation and auto-PEEP in asthmatic and AECOPD patients. Hyperinflation pathophysiology could result in hypotension and barotrauma.[116] This goal is achieved by reducing both respiratory rate and tidal volume. These maneuvers shorten the inspiratory time and lengthen the time for exhalation, resulting in permissive hypercapnia. Permitting hypercapnia in this patient population is safer than causing hyperinflation while attempting to reach a normal $Paco_2$.[103] While intubated, the patient will require scheduled inhalational bronchodilator therapy to reverse the reactive airway disease process. Metered dose inhalers can be used instead of nebulizers, because they may decrease nosocomial pneumonia rates.[107] Deep sedation should be used in an attempt to minimize the use of neuromuscular blockade. Prolonged paralysis linked to neuromuscular blockade has been associated with increases in pneumonia rates and ICU duration of stay.[117]

Extracorporeal Membrane Oxygenation

The last resort in a clinically decompensating asthmatic patient would be the initiation of extracorporeal membrane oxygenation. This technology is considered in those patients who cannot be maintained on mechanical ventilation with adequate oxygenation. Extracorporeal membrane oxygenation requires a dedicated support staff and equipment and is beyond the capabilities of the typical ED.

Treatment Options Beyond the Emergency Department

The following therapies may also be used in the treatment of both severe asthmatic and COPD patients, but there is no evidence to support their use in the acute setting of the ED.

i. Leukotriene modifiers
ii. Mast cell stabilizers
iii. Anti-immunoglobulin therapy
iv. Specific immunotherapy

MANAGEMENT BEYOND THE EMERGENCY DEPARTMENT

Weaning and extubation criteria have not been adequately studied in the acutely asthmatic or AECOPD patient.[103] AECOPD and asthma exacerbations that require ETI typically are slow to resolve and require aggressive therapy for more than 24 hours before weaning and extubation can be considered. Before assessing the patient for possible extubation, the practitioner must confirm that the asthmatic pathophysiologic state that warranted intubation has resolved. First, all sedation and muscle relaxants must be discontinued and prophylactic antiemetic treatment provided. The head of the bed should be raised to greater than 45°. Adequate time must be allowed for the patient to be able to follow simple commands, such as opening his eyes, tracking with his eyes, grasping with both hands, and protruding the tongue on command with no evidence of bronchospasm or hemodynamic compromise. Once appropriate time has elapsed, the cuff leak test should be performed. This test is used to evaluate for any laryngeal edema that might have occurred during the ETI and throughout the treatment. In the absence of laryngeal edema a noticeable airleak should be audible at the patient's bedside when the endotracheal tube cuff is deflated. Zhou and colleagues[118] state that the cuff test is accurate in finding significant differences in laryngeal edema, but that it does not accurately predict the need for reintubation. When no mucosal swelling is evident, the third step is the assessment of oxygenation and ventilation. Adequate oxygenation and ventilation can be assessed with a spontaneous breathing trial on reduced pressure support of 5 cm H_2O. If the patient is able to maintain the following parameters with no bronchospasm, an attempt at extubation can be considered[119]:

- SaO_2 of greater than 92% (Pa_{O_2} >70) on Fi_{O_2} less than 40% and PEEP is less than 5 cm H_2O;
- Tidal volume of greater than 5 mL/kg;
- Mean arterial pressure of greater than 60 with no aid of vasopressor agents;
- Respiratory rate of less than 30 and greater than 6 breaths/min; and
- HR of less than 100 and greater than 60 beats/min.

If the patient remains stable with no evidence of bronchospasm for approximately 30 minutes, one can move forward with the negative inspiratory force test. A value greater than –30 cm H_2O (normal, –90 to –120) indicates that the strength of the

diaphragm and other inspiratory muscles is adequate to attempt extubation. A final assessment modality to predict a successful extubation is the rapid shallow breathing index. This index relies on the idea that patients on a ventilator who cannot tolerate independent breathing tend to breathe with high frequency and shallow tidal volume. Therefore, a score of less than approximately 100 is considered by most an adequate indication of weaning readiness.[120] Upon successful completion of all of these steps, extubation may be undertaken. Safe extubation of a patient requires equipment such as suction, oral airway, supplemental oxygen, and equipment that may be needed if reintubation is required. A nonrebreathing mask and NIV should be at the bedside because extubation may elicit laryngeal edema, bronchospasm, and postextubation stridor that require nebulized epinephrine and further treatment. In short, extubation should always be approached in a logical and cautious manner. Every step should be anticipated meticulously and executed cautiously to prevent reexacerbation or other complications.

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ASTHMA CARE PLANS

The final component of post-AECOPD and asthmatic crisis care is a detailed COPD and asthma care plan that includes explicit discharge instructions, necessary medications and education in how to use them, education in self-assessment, a future action plan for managing recurrence of airflow obstruction, and an explicit follow-up appointment. COPD and asthma care plans, including education and case management, have been associated with improved outcomes and medication compliance. For the patient hospitalized with severe asthma or COPD, it is recommended that follow-up with an asthma/COPD-specialized clinician occur within 1 week of discharge. Pulmonary rehabilitation within the first 4 weeks after AECOPD is recommended to prevent acute exacerbations.[53] The final moments before the patient returns home after an asthmatic or AECOPD crisis are the ideal opportunity for clinicians to provide appropriate care plans that will assist patients with future exacerbations, encourage partnership with primary care physicians, and promote ongoing discussions of home asthma/COPD care.

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