

An Assessment of Therapeutic Regimens in the Treatment of Acute Exacerbations in Chronic Obstructive Pulmonary Disease and Asthma

Grant H. Skrepnek, PhD, RPh; and Stan V. Skrepnek, MD

Abstract

Acute exacerbations in chronic obstructive pulmonary disease (COPD) and asthma are potentially life-threatening clinical events that may result in substantial morbidity and mortality. Treatment of these episodes requires the rapid reversal of airway obstruction by decreasing bronchoconstriction and inflammation. Consensus guidelines and recommendations build on stepwise approaches to care, with the mainstay of therapeutic interventions involving bronchodilators and often including systemic corticosteroids, oxygen, and other treatments, depending on severity and setting. Future therapies that target inflammatory processes may offer improved efficacy and potential disease-modifying effects. The purpose of this article is to assess the treatment options for acute exacerbations in COPD and asthma within the scope of current consensus guidelines and recommendations (eg, Global Initiative for Chronic Obstructive Lung Disease, National Asthma Education and Prevention Program, Global Initiative for Asthma). Although bronchodilators and corticosteroids are the primary therapies discussed, antibiotics, oxygen, magnesium sulfate, noninvasive positive pressure ventilation, and helium/oxygen mixtures are also addressed. Preventive approaches for future exacerbations are considered in the overall approach to achieve optimal outcomes.

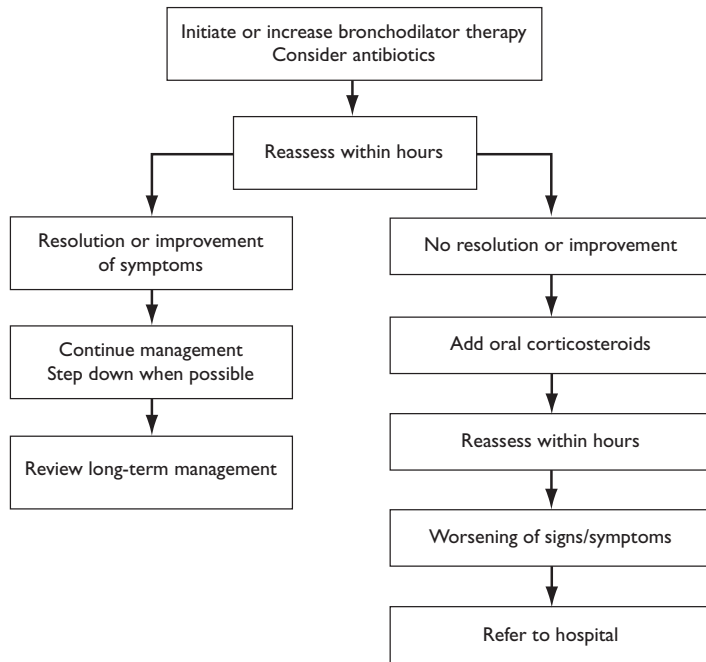
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Exacerbations in chronic obstructive pulmonary disease (COPD) and asthma account for a substantial clinical and economic burden and are often associated with events that ultimately result in morbidity and mortality.¹ As such, guidelines in the overall treatment of both COPD and asthma offer specific recommendations for the management of these acute episodes.

The more recent guidelines for the treatment of COPD published by the National Heart, Lung, and Blood Institute of the National Institutes of Health and the World Health Organization's (NHLBI/WHO) Global Initiative for Chronic Obstructive Lung Disease (GOLD), the American College of Physicians-American Society of Internal Medicine, and the American College of Chest Physicians (ACCP) are based on expert panel consensus and empirical evidence.^{2,3} Although numerous other recommendations have been developed, more recent consensus guidelines for asthma have been developed by the National Asthma Education and Prevention Program (NAEPP) at the NHLBI and through collaborative efforts between NHLBI/WHO's Global Initiative for Asthma (GINA).^{4,9}

Treatment regimens for acute exacerbations generally follow stepwise approaches to therapy with the goals of rapidly reducing airway obstruction and restoring or maintaining lung function. Achieving optimal clinical outcomes through therapeutic approaches requires the consideration of patient characteristics and risk factors, failure of initial treatment, treatment setting, and the severity of the exacerbation itself. Pharmacotherapeutic interventions emphasize the use of bronchodilators, although systemic corticosteroids, oxygen, and numerous other agents may be considered. Prevention and risk-factor modification remain of key importance in long-term care. Many therapies that target underlying inflammatory processes are in development and may offer disease-modifying strategies to reduce the number of substantially pre-

Figure 1. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Algorithm for the Management of an Exacerbation of COPD at Home



Source: Reference 2.
COPD indicates chronic obstructive pulmonary disease.

mature deaths and hospitalizations while improving quality of life in patients with COPD or asthma.

Given the importance of managing COPD and asthma, the purpose of this article is to assess the treatment options for exacerbations within the scope of current consensus guidelines and recommendations. Although an emphasis is placed on the management of these acute events, preventive approaches and future treatments are also highlighted. Providing important background for this discussion, the epidemiology, clinical and economic burden of illness, and clinical presentation of COPD and asthma have been discussed elsewhere in this supplement.¹ The discussion offered herein establishes insight into relevant material; consensus recommendations and additional sources should guide clinical decision making. Many facets beyond exacerbations are important to the management of COPD and asthma,

although these issues are beyond the scope of this article.

General Considerations of Acute Exacerbations in COPD and Asthma

Guidelines for COPD. Several factors must be considered before treating COPD exacerbations. The first is determining the appropriate setting to establish intervention (eg, outpatient, emergency department, hospital admission).¹⁰ Exacerbations are managed by improving airway obstruction by reducing inflammation and bronchoconstriction while promoting mucociliary clearance.¹¹ Comorbid conditions or problems that may precipitate respiratory worsening or failure must also be addressed; if hypoxemia has manifested, it should be rectified.¹² The severity of the exacerbation, treatment failures, comorbidities, and underlying disease characteristics will determine treatment options and the setting in which it is administered.¹³ Careful observation concerning underlying and evolving pulmonary function, particularly in response to therapy, is helpful in determining the need for hospital admission. Outpatient regimens may involve bronchodilators, systemic corticosteroids, and antibiotics; again, a stepwise approach is generally recommended.¹⁴⁻¹⁷ Guidelines for hospital care also consider oxygen therapy and potential mechanical ventilation.² Establishing preventive measures to decrease the likelihood of future exacerbations is a final consideration.

Four aspects of COPD management offered by GOLD involve assessing and monitoring COPD, reducing risk factors, managing stable COPD, and managing exacerbations.² The algorithm for treating acute exacerbations of COPD in outpatient settings appears in **Figure 1**; the **Table** outlines the general considerations of inpatient treatment.

Guidelines for Asthma. GINA recommends that asthma management involve establishing and maintaining control of symptoms, preventing exacerbations and adverse effects of medications, maintaining lung function and normal activity levels, and preventing irreversible airflow limitations and mortality.⁶ The restoration of lung func-

tion and the rapid improvement of both airway obstruction and hypoxia are critical treatment goals for acute exacerbations.⁶ Treatment approaches for these acute cases across guidelines follow stepwise approaches that add additional therapeutic measures when considering the severity of exacerbation; outpatient management emphasizes increasing short-acting β_2 -agonist use and monitoring the response to initial treatment.¹⁸ According to the NAEPP, GINA, and other experts, the primary management of exacerbations within inpatient settings involves increasing the frequency of inhaled short-acting β_2 -agonists, adding systemic corticosteroids, and using oxygen supplementation.^{4-6,19-21} In instances when exacerbations are resistant to initial treatment or are severe in nature, hospital- or emergency department-based monitoring and treatment are recommended.⁶ NAEPP emphasizes the importance of early intervention in asthma exacerbations and directing special attention toward patients at high risk for asthma-related mortality.⁴ Consideration is also placed on reducing the probability of recurrent severe exacerbations and developing written plans to aid in guiding the early management of future exacerbations.

Although NAEPP and GINA generally coincide, clinicians should be aware that certain nuances exist between the 2 guidelines. Recommendations for outpatient management stipulate that the frequency of an inhaled short-acting β_2 -agonist be increased and that continued intensive treatment should be carried out for several days based on severity and response.⁵ **Figure 2** presents the most recent guidelines from GINA on the home management of asthma exacerbations, whereas **Figure 3** focuses on hospital management. More important, development of specific treatment algorithms in acute care settings has been shown to improve patient outcomes and decrease resource consumption.²² A caveat of care in acute asthma involves the use of sedatives; use of these agents is generally contraindicated because of potential respiratory depression and increased mortality.^{5,23,24} Clinicians treating severe cases that require mechanical ventilation and the use of sedatives are directed toward appro-

Table. Global Initiative for Chronic Obstructive Lung Disease (GOLD) Management of Severe but Not Life-Threatening Exacerbations of COPD in the Emergency Department or the Hospital*

Assess severity of symptoms, blood gases, chest X-ray
Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 minutes
Bronchodilators:
Increase dose or frequency
Combine β_2 -agonists and anticholinergics
Consider adding intravenous aminophylline, if needed
Add oral or intravenous glucocorticosteroids
Consider antibiotics:
When signs of bacterial infection, oral or occasionally intravenous
Consider noninvasive mechanical ventilation
At all times:
Monitor fluid balance and nutrition
Consider subcutaneous heparin
Identify and treat associated conditions (eg, heart failure, arrhythmias)
Closely monitor condition of the patient

Source: Reference 2.

COPD indicates chronic obstructive pulmonary disease.

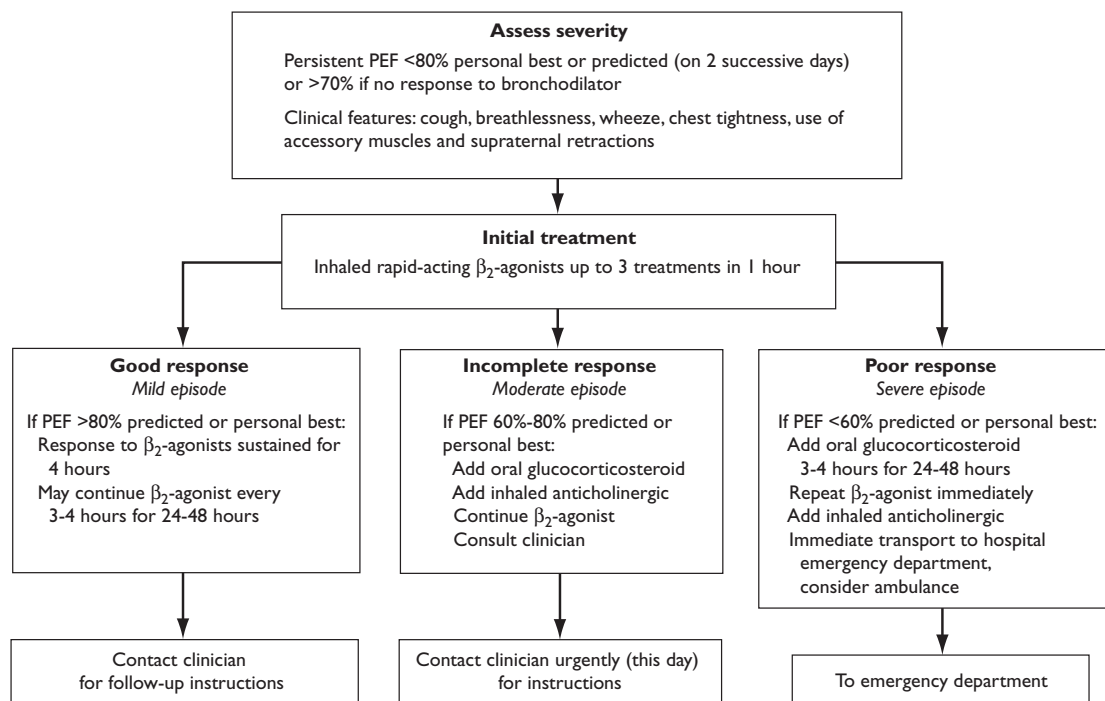
*Local resources need to be considered.

appropriate references for additional information for monitoring and intervention.^{5,6,25}

Therapeutic Considerations in Management and Treatment

Bronchodilators. The primary therapy for overall COPD and related exacerbations is inhaled bronchodilator therapy.^{2,14,15,26} Bronchodilators recommended specifically for COPD exacerbations include short-acting β_2 -agonists (eg, albuterol, levalbuterol, bitolterol, pirbuterol) and anticholinergics (eg, ipratropium bromide). Outpatient management typically involves increasing the dose and/or frequency of agents prescribed to the patient, whereas inpatient therapy relies on short-acting β -agonists by GOLD standards.² A meta-analysis indicated that no significant differences in improved forced expiratory volume in 1 second (FEV₁) were noted in COPD exacerbations between the β_2 -agonists and ipratropium, although the β_2 -agonists that were included may have worsened the arterial blood gas profile in the hours immediately following initial patient presentation.²⁷ Delivery via a

Figure 2. Guidelines for the Home Management of Acute Exacerbations in Asthma Offered by Global Initiative for Asthma (GINA)*



Source: Reference 6.

PEF indicates peak expiratory flow.

*Patients at risk for asthma-related death should contact clinician promptly after initial treatment. Additional therapy may be required.

metered dose inhaler (MDI) and spacer has been reported to produce similar effects as nebulization, although certain studies specific to asthma have noted that MDIs with a spacer may provide a more rapid onset to lessen time spent in emergency departments.²⁸⁻³⁰ The use of long-acting β_2 -agonists (eg, salmeterol, formoterol) is generally reserved for maintenance treatment of COPD.^{2,31,32} Taken from Bach and colleagues,³³ the following was concluded in their review of 14 randomized trials concerning bronchodilator use in COPD:

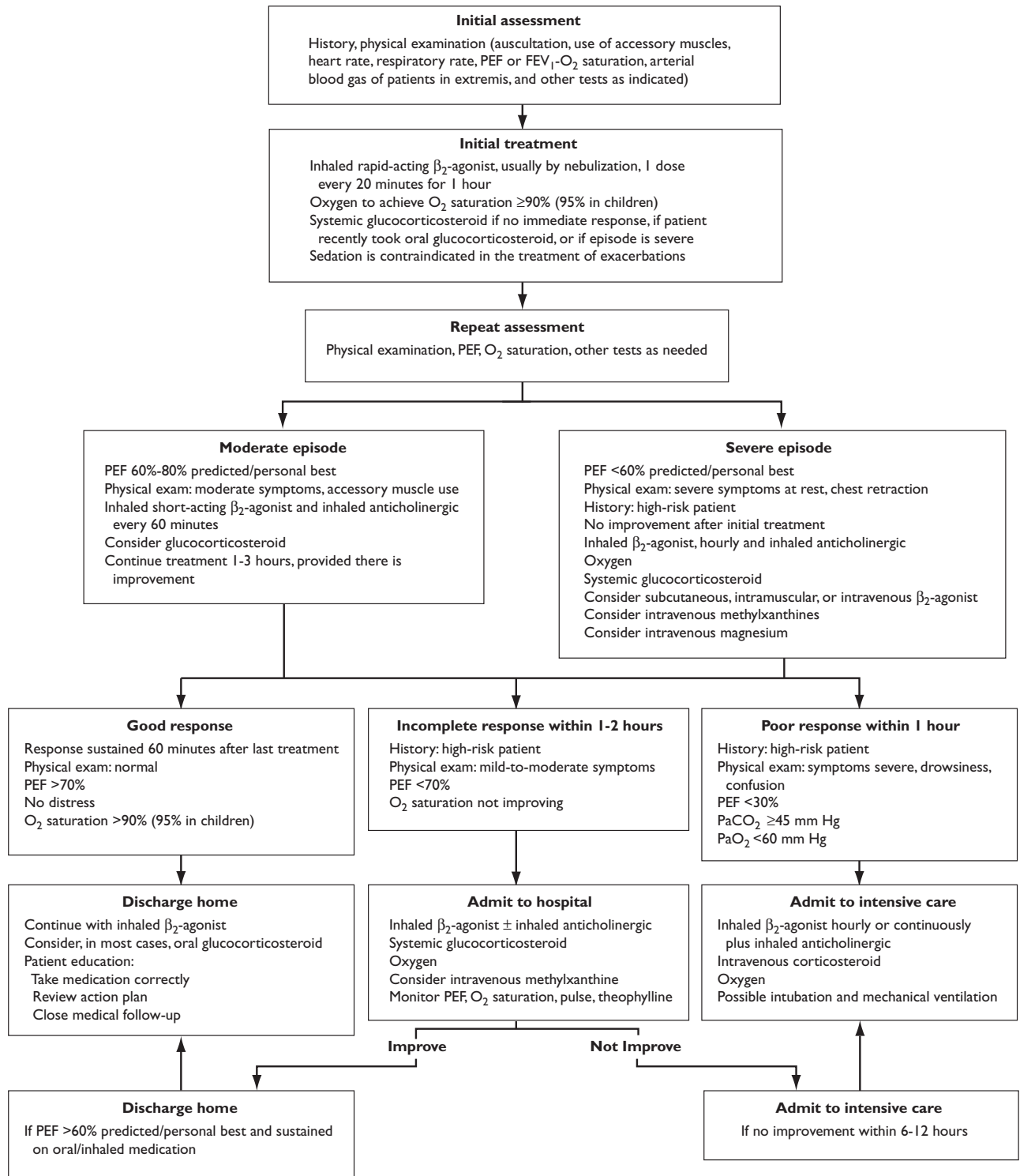
“Short-acting β -agonist-type and anticholinergic-type inhaled bronchodilators have similar effects on spirometry and a greater effect than all parenterally administered bronchodilators (ie, parenteral methylxanthines and sympathomimetics); the toxicity profile of the methylxanthine agents makes them potentially harmful; and some patients may experience additional benefits when a second

bronchodilating agent is administered after the maximal dose of the initial inhaled bronchodilator is reached.”³³

Tiotropium bromide, a long-acting muscarinic receptor M_1 - and M_3 -selective anticholinergic agent, has demonstrated in international clinical trials improved efficacy relative to ipratropium as well as salmeterol in the treatment of stable COPD.³⁴⁻³⁷ Decreases in exacerbations in COPD have been observed with the once-daily dosed medication.^{38,39} Given the long-acting nature of tiotropium, however, its use in the emergent care of acute exacerbations of either COPD or asthma has yet to be established. Currently, no newer short-acting anticholinergic agents are in an advanced development phase.⁴⁰

According to NAEPP and GINA, inpatient care of exacerbations in asthma emphasizes the use of inhaled short-acting β_2 -agonists, whereas systemic β_2 -agonists (eg, epinephrine, terbutaline) should only be con-

Figure 3. Guidelines for the Hospital Management of Acute Exacerbations in Asthma Offered by the Global Initiative for Asthma (GINA)*



Source: Reference 6.

FEV₁ indicates forced expiratory volume in 1 second; PEF, peak expiratory flow; PaO₂, arterial pressure of oxygen; PaCO₂, arterial pressure of carbon dioxide.

*Preferred treatments are inhaled β₂-agonists in high doses and systemic glucocorticosteroids. If inhaled β₂-agonists are not available, consider intravenous aminophylline.

sidered in very severe or nonresponsive cases.^{5,6,20,21} Research has found either equal or improved efficacy with aerosolized β_2 -agonists versus systemic agents in acute asthma, also noting an improved safety profile and lower potential for toxicity.⁴¹ Combined treatment with both intravenous and nebulized β_2 -agonists is not warranted.⁴² The routine use of continuous nebulization, although commonplace, has not been empirically established as a preferred management strategy relative to intermittent treatment.⁴³ The long-acting β_2 -agonists (eg, salmeterol, formoterol) are generally not recommended for emergent care of acute asthma.^{25,44}

Opinion and research have indicated that the use of ipratropium in an adjunctive role with β_2 -agonist regimens for acute exacerbations in asthma may improve airflow, particularly in more severe cases.^{21,45} NAEPP and GINA consider the addition of ipratropium to β_2 -agonists for emergency department and hospital-based care of asthma exacerbations, and GINA guidelines state that the use of ipratropium with β_2 -agonist treatment should be considered before methylxanthines because of potentially lower hospitalization rates and improvement in peak expiratory flow and FEV₁.⁴⁻⁶ However, uniform support does not yet exist concerning the routine addition of ipratropium with β_2 -agonists in acute asthma, although some experts state that the concomitant approach may appear to be a beneficial first-line strategy in severe adult asthma.^{25,46-50} Thus, the therapeutic placement of the agent is generally recommended only as an adjunctive approach in patients who are not responsive to β_2 -agonist therapy alone.^{4,48,51,52} In children, research has noted that all individuals receiving intensive emergency department treatment did not receive benefit when ipratropium was added to β_2 -agonist and corticosteroid therapy; however, other literature suggest that ipratropium offers clinical improvements, particularly in more severe cases.^{6,21,53-57}

The side-effect profile of ipratropium has been purported to be milder than β -agonists, with fewer number and frequency of side effects being reported.^{33,46,58} Within the class of short-acting β -agonists, albuterol is the

most commonly used agent, and side effects are dose-dependent.^{25,44,59} Recent evidence suggests that levalbuterol (R-albuterol) may be associated with lower toxicity, higher efficacy, and decreased length of hospital stays when compared with racemic albuterol, and the single isomer may have potential use in COPD, asthma, and related exacerbations; its use has also been noted in children.⁵⁹⁻⁶⁵ Although evidence presented primarily from preclinical models found that S-albuterol is associated with pharmacologic effects and may enhance smooth muscle contraction and airway hyperresponsiveness, clinical trials have suggested that the S-isomer may be clinically inert.⁶⁶⁻⁶⁸ Other clinical findings may be indicative of negative effects associated with the S-isomer; additional study is warranted to establish more robust conclusions.^{59,63,64,69} If high-dose β_2 -agonist therapy is used with albuterol in acute asthma, appropriate delivery and administration methods should be selected to minimize side effects and toxicity.^{22,25}

The methylxanthines (eg, aminophylline, theophylline) are considered efficacious bronchodilators, although the narrow therapeutic window and side-effect profile limit their use in exacerbations of COPD and asthma.^{2,4-6} Recent meta-analyses for both COPD and asthma exacerbations found no consistent benefit from methylxanthines, yet an increase in adverse events was observed.^{70,71} Of all the guidelines discussing COPD exacerbations, only older guidelines recommended the use of methylxanthines in COPD exacerbations when inhaled bronchodilators provide inadequate therapy.¹⁵ In acute asthma, GINA guidelines suggest that the use of these agents be considered only during severe exacerbations and remain an alternative therapy.^{6,71} NAEPP does not recommend methylxanthine use in emergency departments or hospital settings, and the use of these agents was controversial for adults while offering little benefit but increased risk to children.^{4,5,72}

Systemic Corticosteroids. Systemic corticosteroids (eg, prednisone, prednisolone, methylprednisolone) are considered effective in both inpatient and outpatient settings for the treatment of COPD exacerbations by

accelerating recovery time and lung function while decreasing relapse rates; meta-analyses have found the therapies to offer short-term improvement for exacerbations, although the analyses also addressed increased risks for adverse drug reactions associated with the class.⁷³⁻⁷⁷ GOLD suggests the addition of systemic corticosteroids to bronchodilators if moderate-to-severe COPD is present and as a general recommendation for inpatient care.⁵ These guidelines also state that nebulized budesonide may offer an alternative to oral agents in outpatient management in the absence of respiratory acidosis.^{2,78} Continued study is warranted concerning the use of corticosteroids in outpatient venues, particularly with optimum dosing and duration.³³ For long-term treatment in COPD, a meta-analysis found inhaled corticosteroids to slow the progression of pulmonary function decline dramatically, although others had considered the class to offer minimal clinical benefit in COPD.^{79,80}

Although they are not recommended routinely in acute asthma treatment, corticosteroids (eg, beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone) may either be initiated or the frequency increased under certain circumstances for outpatient management of exacerbations.⁴ The GINA guidelines address the role of inhaled corticosteroids in already-developed exacerbations, and reviews of clinical studies have reported improved bronchodilation and decreased relapse rates with early use in milder cases.^{6,81-83} Conflicting results from clinical trials exist concerning the use of inhaled corticosteroids in acute asthma, however, some clinicians strongly caution against routine use, particularly in children.^{81,84-86} Less debatable is the use of systemic administration of corticosteroids in more moderate or severe exacerbations in home management. GINA, NAEPP, and other experts place systemic corticosteroids administered via oral or intravenous routes as an integral component of inpatient care for all but mild exacerbations. A meta-analysis found the early use of systemic corticosteroids to significantly decrease hospital admissions from emergency departments.^{4,6,87,88} The choice of intravenous versus oral dosage forms does not appear to

offer a difference in efficacy, which is an important consideration in their use by children.^{89,90} Precise dosing and schedules have not been established, yet high doses do not appear to provide added clinical benefit.⁷⁹

Antibiotics. Although approximately one third of COPD exacerbations are either viral in nature or have no identifiable etiology, antibiotics are generally recommended if worsening dyspnea is accompanied by increased sputum production and/or change in sputum purulence.^{91,92} Evidence has also suggested that more severe cases of COPD exacerbations are afforded the greatest improvement in clinical outcomes with antibiotic therapy.⁹³ GOLD recommends that the spectrum of activity should echo local patterns of sensitivity concerning *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.² Concerns addressing drug resistance and relapse rates, especially in patients with severe COPD, have been investigated and addressed in the literature.¹³

Similar to COPD recommendations by GOLD, both NAEPP and GINA do not primarily recommend antibiotic use for asthma exacerbations except in instances for which comorbid conditions or the presence of fever, sputum changes, or suspected pneumonia or bacterial sinusitis warrant their use.^{4,6} A meta-analysis of the role of antibiotics in acute asthma noted many challenges in interpreting results from disparate literature and indicated that established consensus recommendations would likely remain until more robust empirical assessments are made.⁹⁴ The role of bacterial infections in acute asthma is believed to be small, although atypical bacteria including *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* have been found in some exacerbations.⁹⁵ Viral respiratory infections, particularly from rhinovirus, have been reported to play a major role in precipitating asthma exacerbations, with virus-induced acute asthma potentially warranting special management considerations.⁹⁶⁻⁹⁸

Oxygen. In moderate-to-severe exacerbations of COPD, hypoxemia is considered a primary concern in regard to morbidity.

When patients present to an inpatient setting or emergency department with exacerbations, their initial therapy should be controlled oxygen as recommended by GOLD. Oximetry is helpful for determining the need and success of oxygen therapy. Oxygen therapy has been associated with increases in survival.^{2,51} Although oxygen therapy has been found to worsen hypercapnia and can result in pulmonary failure, the beneficial effects of the therapy on respiratory and cardiovascular function are often considered to outweigh the risks.³³ Because of clinical concerns, however, identification of patients at highest risk for hypercapnia has been suggested.³³ In the treatment of asthma exacerbations, especially in more moderate-to-severe cases, oxygen therapy is an important supportive care measure in emergency department or hospital settings and is generally recommended for most patients.^{5,6,21,25}

Magnesium Sulfate. Intravenous magnesium sulfate, which relaxes smooth muscle causing bronchodilation, is considered adjunctive therapy for acute severe asthma, with collective assessments of clinical trials not necessarily demonstrating a clear benefit for routine use in emergency department settings.^{6,21,99,100} In certain patients with poor response to β_2 -agonists or with adults whose FEV₁ on presentation is from 20% to 30% predicted, some benefit has been demonstrated. GINA guidelines confirm the use of intravenous magnesium sulfate for the hospital management of severe episodes of asthma exacerbation.^{6,101}

Noninvasive Positive Pressure Ventilation. Noninvasive positive pressure ventilation (NIPPV) has demonstrated efficacy in respiratory failure among a wide range of diseases.¹⁰² In cases of respiratory failure related to COPD exacerbations, NIPPV has been found to shorten hospital stays and improve survival rates and offers an important alternative to intubation or mechanical ventilation.¹⁰³ Overall, the treatment may be used in intensive care or hospital settings with appropriate training of personnel.¹⁰⁴ The use of NIPPV in acute exacerbations of asthma is less clear than in COPD, although some research indicates decreased hospital-

ization rates and improved pulmonary function.^{105,106} Expert panels have recommended that a more comprehensive evaluation of NIPPV is needed from clinical trials.¹⁰⁷ It has been suggested that NIPPV use be limited to cases of impending respiratory failure or as an alternative to intubating patients with acute asthma.²⁵

Mucolytics and Expectorants. The use of mucolytic agents in COPD exacerbations is an area warranting additional research by GOLD.² Although a meta-analysis has indicated potential benefits based on reduction in exacerbations and in disability days in stable COPD, the agents are generally not considered in the routine management of acute exacerbations.¹⁰⁸ NAEPP and GINA guidelines coincide with older recommendations on the use of inhaled mucolytic agents for asthma exacerbations. Furthermore, they do not recommend the regimens because of a lack of consistently demonstrated benefit and concerns of the risk associated with worsened airway obstruction and cough, particularly in more severe cases.^{4,6,21}

Heliox. Small trials of combined helium and oxygen (heliox) in COPD exacerbations have shown some improvement in respiratory function in inpatient settings.¹⁰⁹ Heliox is not addressed in the GOLD guidelines for COPD exacerbations.² For asthma, clinical studies have generally indicated that the combination does not necessarily improve lung function in mild or moderate asthma exacerbations relative to standard therapy, a finding that was also offered from broad meta-analyses concerning the therapy.^{110,111} GINA guidelines for asthma state that the mixture may be best reserved for patients presenting with more severe disease, and that routine use in other cases is unwarranted.⁶

Leukotriene Antagonists. Leukotriene antagonists (eg, montelukast, zafirlukast, zileuton) are used primarily for the long-term management of asthma.¹¹² Initial findings and opinions from clinical trials in acute asthma, however, may provide evidence for a potential role in their use based

on improvements in symptoms and pulmonary function; the overall cost effectiveness in acute asthma, however, has been questioned.¹¹³⁻¹¹⁵ No consensus currently exists concerning the use of these agents in acute asthma, and additional investigation is warranted concerning their role in the treatment of exacerbations.¹¹⁶

Prevention

A strategy encompassing continuous, long-term, comprehensive care with appropriate clinician follow-up should be sought to prevent or reduce future exacerbations in both COPD and asthma. No therapy exists that substantially modifies the long-term progression of COPD.² As such, risk-factor modification, particularly smoking cessation, is pertinent to ease the progression of the disease, although patient education, influenza vaccination, and potential pulmonary rehabilitation are also important.^{2,117,118} GOLD generally recommends that the treatment of stable COPD follows a stepwise approach based on severity and often involves bronchodilators, exercise, and, occasionally, corticosteroids.² Methods to both increase patient adherence to the complex therapies in COPD and selecting appropriate interventions have also been emphasized.¹¹⁹ Hospital discharge recommendations often involve monitoring of therapeutic interventions and lung function, increased patient education, risk modification, discussion of barriers to care or disabilities, and follow-up care.²

Overall recommendations concerning the prevention of future exacerbations in asthma include developing management partnerships between clinicians and patients, education, appropriate assessment and monitoring, establishing plans for medication use and for treating exacerbations, minimizing risk factors, and routine follow-up care.^{5,6}

Discharge from emergency department or hospital settings should involve detailed information concerning appropriate medication use, management, monitoring, and follow-up care.⁶ Discharge use of oral corticosteroids has been shown to reduce the frequency of relapses (NAEPP). Inhaled steroids have been specifically shown to

reduce subsequent exacerbations after an acute asthmatic episode.¹²⁰⁻¹²² Long-term control of asthma may also include agents such as long-acting inhaled β_2 -agonists (eg, salmeterol, formoterol), leukotriene receptor antagonists, cromolyn, nedocromil, or combination products (eg, fluticasone/salmeterol).⁵ Management by allergy specialists has also been shown to reduce the likelihood of asthma exacerbations.¹²³⁻¹²⁹

Future Treatment Options

Statements of future areas of research in COPD have addressed the need for a more detailed understanding of the specific surrogate markers and mechanisms involved in the inflammatory component of the disease to aid in the identification of at-risk patients and in the development of new treatments.² Ultimately, methods to potentially reverse COPD and promote alveolar regrowth require advances in numerous areas. The role of inflammatory processes in both the prevention and treatment of exacerbations in COPD has been discussed elsewhere.¹³⁰⁻¹³³ Based on recent advances in the understanding of the pathogenesis of inflammation in COPD, numerous agents that may be used to treat COPD are being studied, including those that may offer disease-modifying properties. Specifically related to research with new agents for COPD, mixed findings have been observed involving leukotriene inhibitors, protease inhibitors (ie, α_1 -antitrypsin, neutrophil elastase), and matrix metalloproteinase inhibitors.¹³⁰⁻¹³³ Although cytokine inhibitors targeting mediators of inflammation (eg, interleukin [IL]-8, IL-10, tumor necrosis factor [TNF]- α) have generated considerable interest with application to COPD, concerns of cost and safety have also accompanied the agents.¹³⁰⁻¹³³ Additional study is warranted concerning phosphodiesterase-4 inhibitors (eg, cilomilast), retinoids, antioxidants, and mucous regulators (ie, P2Y₂ purinergic-receptor agonists, tachykinin antagonists).¹³¹⁻¹³³

In asthma, research has also been directed toward identifying at-risk patients, in understanding inflammatory mechanisms of the disease, and in developing new treatment options.^{6,134,135} Cytokine and chemokine inhibition or modulation has been

investigated to target interleukins (eg, IL-4, IL-5, IL-13), TNF- α , interferons (eg, interferon [INF]- γ , INF- α), and eosinophils.¹³⁴⁻¹³⁷ Mediator antagonists (eg, mast cell tryptase, platelet activating factor, tachykinins, thromboxane) may offer treatment options, although limited potential has been observed in asthma for some of the agents.^{6,134,138} Phosphodiesterase-4 inhibitors (eg, cilomilast, roflumilast) and α_4 integrin antagonists are also potential targets for therapy.^{134,135,139,140} Studies with ozalimumab, an immunoglobulin E-specific monoclonal antibody for use in moderate-to-severe persistent asthma, have indicated that decreased asthma exacerbations and reductions in corticosteroids accompanied the treatment.¹⁴¹

Conclusion

Acute exacerbations in COPD and asthma represent potentially life-threatening clinical events that require appropriate diagnosis, treatment, and monitoring in both inpatient and outpatient settings. Guidelines for the management of exacerbations in COPD and asthma are built on consensus and consider therapies as a function of the response to initial treatment, exacerbation severity, treatment setting, and underlying patient characteristics and risk factors. Although standard agents used in exacerbations of both conditions involve bronchodilators, systemic corticosteroids, and oxygen, there are several novel agents being investigated that address the inflammatory mechanisms of the conditions. Future research is required in several areas to offer improved patient care and to minimize associated morbidity and mortality. However, more consistent use of currently available modalities for persistent asthma, such as inhaled corticosteroids, should be considered.^{120-122,129,142-148}

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