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The Acute Management of Asthma

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Abstract Patients presenting to the emergency department (ED) or clinic with acute exacerbation of asthma (AEA) can be very challenging varying in both severity and response to therapy. High-dose, frequent or continuous nebulized short-acting beta$_2$ agonist (SABA) therapy that can be combined with a short-acting muscarinic antagonist (SAMA) is the backbone of treatment. When patients do not rapidly clinically respond to SABA/SAMA inhalation, the early use of oral or parenteral corticosteroids should be considered and has been shown to impact the immediate need for ICU admission or even the need for hospital admission. Adjunctive therapies such as the use of intravenous magnesium and helium/oxygen combination gas for inhalation and for driving a nebulizer to deliver a SABA and or SAMA should be considered and are best used early in the treatment plan if they are likely to impact the patients' clinical course. The use of other agents such as theophylline, leukotriene modifiers, inhaled corticosteroids, long-acting beta$_2$ agonist, and long-acting muscarinic antagonist currently does not play a major role in the immediate treatment of AEA in the clinic or the ED but is an important therapeutic option for physicians to be aware of and to consider initiating at the time of discharge from clinic, hospital, or ED to reduce later clinical worsening and readmission to the ED and hospital. A comprehensive summary is provided of the currently available respiratory pharmaceuticals approved for asthma and other airway syndromes. Clinicians must be prepared to use the entire spectrum of medications available for the treatment of acute asthma exacerbations and the agents that should be initiated to prevent worsening or additional exacerbations. They need to be familiar with the major potential drug toxicities associated with their use.

Keywords Asthma · Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS) · Theophylline · Beta$_2$ agonists · Muscarinic antagonists · Corticosteroids · Inhaled corticosteroids · Leukotriene modifiers · Omalizumab · Asthma treatment in the emergency department (ED) · 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel 3 guidelines

Abbreviations

ED	Emergency department
AEA	Acute exacerbations of asthma
USA	United States of America
COPD	Chronic obstructive pulmonary disease
ACOS	Asthma-chronic obstructive pulmonary disease-overlap syndrome
SABAs	Short-acting beta$_2$ agonists
FDA	US Food and Drug Administration
Arg	Arginine
Gly	Glycine
ADB$_2$R-B16	Amino acid 16 in the adrenergic B$_2$R gene
LABAs	Long-acting beta$_2$ agonists
SAMA	Short-acting muscarinic antagonist
ICS	Inhaled corticosteroids
NAEPP	2007 National Asthma Education and Prevention Program
LAMAs	Long-acting muscarinic antagonists

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SC	Systemic corticosteroids
GR	Glucocorticoid receptor
LTRA	Leukotriene receptor antagonists
M2	Muscarinic receptor 2
M3	Muscarinic receptor 3
PDE	Phosphodiesterase
iv	Intravenous

Introduction

The emergency department (ED) or clinic treatment of acute exacerbations of asthma (AEA) can be a challenge. The patients range from minor exacerbations to the sickest of asthma patients with frequent exacerbations that require large dosages of medications and result in high healthcare utilization and expenses (Table 1) [1]. Many of these patients have severe persistent and poorly controlled asthma with no outpatient follow-up [2, 3]. It is estimated that there were 2.1 million asthma-related ED visits in 2009 [4, 5] and 1.8 million asthma-related ED visits in 2010 in the United States of America (USA) [6]. There are an estimated 25.7 million persons in the USA with asthma [7]. Hospitalization rates from the ED range from 11 % in Canada to 21 % in the USA in a prospective cohort study [8]. A recent study in North Carolina found that many patients use the ED for routine asthma care. They often have mild, intermittent asthma and lack a source for primary care [9].

A proportion of the more complex asthmatic patients presenting to the ED include those with the recently described phenotype known as the asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) [10–13]. These atopic smokers experience very frequent and severe exacerbations at an earlier age than typical COPD patients and tend to respond to both asthma and COPD treatment options. Most guidelines on the treatment of asthma have avoided specific recommendations in the treatment of ACOS patients. Further, most clinical trials have not included these patients. A detailed discussion of ACOS exacerbation treatment options is not given as they currently do not differ from those of AEA.

Guidelines and reviews for the treatment of AEA are available [2, 3, 14–16]. This paper focuses on the pharmacology, side effects, and efficacy data of medications both approved by the USA Food and Drug Administration (FDA) and those used off-label for the ED treatment of AEA. The goals of ED asthma treatments include reducing the need for hospitalization and mechanical ventilation and the frequency of relapse after discharge from the ED, improving the quality of life, minimizing adverse drug events, and maximizing patient safety.

Short-Acting Beta$_2$ Agonists (SABAs)

Inhaled SABAs are "relief" or "rescue" medications and the cornerstone therapy for AEA in the ED [3, 14, 15, 17]. These

Table 1 Severity classification of acute asthma exacerbations in the clinic or ED modified from NAEPP Expert Panel 3 guidelines [3]

Classification	Signs and symptoms	Initial PEF (or FEV_1)	Clinical course
Mild	Dyspnea only with activity, wheezing	PEF>70 % predicted or personal best	▪Usually treated at home ▪Prompt relief with inhaled SABA ▪Possible short course of oral CS
Moderate	Dyspnea interferes with or limits usual activity, wheezing	PEF 40–69 % predicted or personal best	▪Usually requires urgent office or ED visit ▪Relief from inhaled SABA (frequent or continuous) ▪Consider short course of oral CS
Severe	Dyspnea at rest; interferes with speaking full sentences, decreased breath sounds, reduced wheezing	PEF<40 % predicted or personal best	▪Usually requires emergent ED visit and likely results in hospitalization ▪Partial or no relief from inhaled SABA ▪Requires frequent or constant inhaled SABA + SAMA ▪Early systemic (oral, iv, or im) CS ▪Consider adjunctive therapy (magnesium iv, Heliox nebulization of SABA + SAMA, etc.)
Subset: life-threatening	Too dyspneic to speak, perspiring, may lack air movement, and wheezing	PEF<25 % predicted or personal best	▪Requires ED visit and will need hospitalization, likely ICU ▪Minimal relief for inhaled SABA ▪Will require frequent or constant inhaled SABA/SMA ▪Early iv CS ▪Possible intubation ▪Early adjunctive therapies (magnesium iv, Heliox nebulization of SABA + SAMA, etc.)

PEF peak expiratory flow, *ED* emergency department, *SABA* short-acting beta$_2$ agonist, *SAMA* short-acting muscarinic antagonist, *CS* corticosteroids, *iv* intravenous, *im* intramuscular, *ICU* intensive care unit

bronchodilators act on beta$_2$ airway receptors (B_2R) leading to relaxation of airway smooth muscles and airflow improvement. SABAs are the most effective bronchodilators to promptly reverse bronchoconstriction during AEA. The cellular action of SABAs/long-acting beta$_2$ agonists (LABAs) is through the stimulated B_2R's ability to modulate intracellular adenylyl cyclase generating cyclic adenosine monophosphate which then activates effector protein kinases and guanine nucleotide exchange functions [18].

Currently, racemic albuterol and levalbuterol are the only SABAs available as metered-dose inhalers (MDIs) after the required conversion to hydrofluoralkane propellant. Albuterol and levalbuterol are also available for nebulization (Table 2). Although individuals vary, overall using albuterol MDI with a disposable spacer is not inferior to nebulized albuterol in AEA [19]. The ED time was significantly shorter by almost a half an hour in children treated with a SABA and a spacer compared to without a spacer. The use of spacers was limited by lack of availability and the perceived cost of spacers in a study in Canada despite the fact that most ED staff believed they are effective [20].

The frequency of delivery of nebulized albuterol to achieve clinical effects was addressed in a meta-analysis of six trials which concluded that there is no clinical difference between albuterol given by continuous or frequent intermittent nebulization (every 20–60 min) in the treatment of AEA [21]. This is in contrast to a Cochrane review of eight trials which compared continuous to intermittent SABA delivery and reported reduced admissions and improved pulmonary function without inducing a tachycardia, tremor, or hypokalemia in adults with AEA [22]. Continuous SABA treatment is safe, requires less clinical labor, and may have increased efficacy compared to the intermittent SABA approach in the most severe AEA patients.

Although not directly compared to albuterol, no efficacy or adverse effect differences were found between nebulized epinephrine (an alpha$_1$, beta$_1$, and B_2R agonist) and the SABA terbutaline in adults with severe AEA [23, 24]. No routine role has been demonstrated in treating AEA in the ED with inhaled use of these agents. Both subcutaneous epinephrine and terbutaline have been used in the treatment of AEA in a small 20 patient double-blinded study. No significant difference in spirometry, heart rate, blood pressure, degree of pulsus paradoxus, or continuous electrocardiograms was found between subcutaneous 0.5 mg epinephrine compared to 0.5 mg terbutaline [25]. The use of subcutaneous epinephrine or terbutaline in AEA is not recommended in most guidelines and should be limited to the most severe cases of AEA not benefiting from inhaled therapy.

Compounding the difficulty of treating asthma patients, paradoxical bronchospasm, and increased bronchial hyperresponsiveness can be seen with both albuterol and levalbuterol treatments in asthma patients [26]. The cause is unknown but may relate to diluents, pharmacogenetics, and polymorphisms of patients that are currently poorly understood. Polymorphism with homozygosity of arginine (*Arg/Arg*) rather than the normal glycine (*Gly/Gly*) at amino acid 16 in the adrenergic B_2R gene (*ADB$_2$R-B16-Arg/Arg* patients) coding region reduces the long-term response to albuterol. Additional genetic polymorphisms appear to exist and alter the functional properties of the B_2R changing the responsiveness to SABAs/LABAs [27]. In addition, with constant stimulation, downregulation of the B_2R to SABAs can limit the usefulness of these agents by causing tachyphylaxis manifested as a decrease in bronchodilation. These genetic and receptor changes may explain some of the refractory patients seen in the ED.

Adverse effects with SABAs include increased heart rates, palpitations, tachyarrhythmias, and driving potassium intracellular leading to the development of hypokalemia [18]. Hypokalemia-induced ventricular arrhythmias have been reported, but arrhythmias can also be precipitated by high-dose SABA therapy independent of hypokalemia. Studies comparing the effect of racemic albuterol to levalbuterol in intensive care patients and pediatric cardiology patients demonstrated small but similar increases in heart rates with both SABAs [28, 29]. A recent systematic review and meta-analysis examining levalbuterol and albuterol in acute asthma failed to demonstrate improved efficacy or safety with levalbuterol [30]. SABAs can also stimulate liver glycogenolysis which can result in hyperglycemia. Tremors from direct B_2R stimulation in the skeletal muscle are common and can limit chronic acceptance of SABA therapy by the patient but is rarely an acute limiting factor. The direct SABA stimulation of the arterial B_2R can result in vasodilation and hypotension that further drives a reflex tachycardia. A syndrome of SABA-induced type B lactic acidosis is reported in treated asthmatics resulting from many mechanisms including endogenous and exogenous hyperadrenergic states [31].

Long-Acting Beta$_2$ Agonists (LABAs)

For long-term use, LABAs remain the preferred add-on drug to inhaled corticosteroids (ICS) in the 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel 3 guidelines for longer term treatment of children and adults [3, 17]. There is no role for acute use of LABAs in the clinic or ED treatment of AEA, but initiation may be considered at the time of discharge in patients with frequent clinic or ED visits or with persistent asthma on ICS.

The exact mechanism leading to longer duration of action of the LABAs is not known but may be from their lipophilicity, agonist efficacy, and unique micro-kinetic behaviors [18, 32, 33]. As a result, twice a day dosing with the oldest LABAs (salmeterol, arformoterol, and formoterol) and once a day

Table 2 Current treatments for acute asthma/ACOS/COPD exacerbations in the clinic, ED, or at discharge

Drug	Dose (base equivalent)[a]	Route	Frequency	Comments
Short-acting beta$_2$ agonists (SABA)				
Albuterol sulfate	2 and 4 mg tabs	Oral	q6-8H	Various generics[b]
Albuterol sulfate	4 and 8 mg ext tabs	Oral	bid	Various generics[b]
Albuterol sulfate	2 mg/5 ml syrup	Oral	q6-8H	Various generics[b]
Albuterol sulfate	0.5 % or 2.5 mg/0.5 ml	Inhalation/neb	Max 0.5 mg q4H	Various generics[b]
Albuterol sulfate	0.083 % or 2.5 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Various generics[b]
Terbutaline	2.5 and 5.0 mg tabs	Oral	prn, q6H-cont.	Various generics[b]
Terbutaline	1 mg/ml	Injection	prn, q6H-cont.	Various generics[b]
Levalbuterol	0.01 % or 0.3 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Various generics[b]
Levalbuterol	0.01 % or 0.3 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Xopenex®[b]
Levalbuterol	0.02 % or 0.63 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Various generics[b]
Levalbuterol	0.02 % or 0.63 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Xopenex®[b]
Levalbuterol	0.04 % or 1.25 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Various generics[b]
Levalbuterol	0.04 % or 1.25 mg/3 ml	Inhalation/neb	prn, q6H-cont.	Xopenex®[b]
Levalbuterol	0.25 % or 1.25 mg/0.5 ml	Inhalation/neb	prn, q6H-cont.	Various generics[b]
Levalbuterol	0.25 % or 1.25 mg/0.5 ml	Inhalation/neb	prn, q6H-cont.	Xopenex®[b]
Albuterol sulfate	0.09 mg/inhalation	MDI	prn, Q6H-q1H	Proventil HFA®[b]
Albuterol sulfate	0.09 mg/inhalation	MDI	prn, Q6H-q1H	Ventolin HFA®[b]
Albuterol sulfate	0.09 mg/inhalation	MDI	prn, Q6H-q1H	ProAir HFA®[b]
Levalbuterol tartrate	0.045 mg/inhalation	MDI	prn, Q6H-q1H	Xopenex HFA®[b]
Long-acting beta$_2$ agonists (LABA)				
Formoterol fumarate	0.02 mg/2 ml	Inhalation/neb	bid	Perforomist®[d]
Arformoterol tartrate	0.015 mg/2 ml	Inhalation/neb	bid	Brovana®[d]
Formoterol fumarate	0.012 mg/inhalation	Dry powder	bid	Foradil®[c, d]
Salmeterol xinafoate	0.05 mg/inhalation	Dry powder	bid	Serevent Diskus®[c, d]
Indacaterol maleate	0.075 mg/inhalation	Dry powder	qd	Arcapta®[d]
Olodaterol	0.005 mg/inhalation	SDM	qd	Striverdi Respimat®[d]
Short-acting muscarinic antagonists (SAMA)				
Ipratropium bromide	0.5 mg/3 ml	Inhalation/neb	q6–8H	Various generics[d]
Ipratropium bromide	0.021 mg/inhalation	MDI	qid	Atrovent HFA®[d]
Long-acting muscarinic antagonists (LAMA)				
Tiotropium bromide	0.018 mg/inhalation	Dry powder	qd	Spiriva Handihaler®[d]
Aclidinium bromide	0.375 mg/inhalation	Dry powder	bid	Tudorza Pressair®[d]
Combination bronchodilators (SABA + SAMA)				
Albuterol sulfate + ipratropium	2.5 mg+0.5 mg/3 ml	Inhalation/neb	qid	Duoneb®[d]
Albuterol sulfate + ipratropium bromide	2.5 mg+0.5 mg/3 ml	Inhalation/neb	qid	Various generics[d]
Albuterol sulfate + ipratropium bromide	0.1 mg+0.03 mg/inhalation	SDM	qid	Combivent Respimat®[d]
Combination bronchodilators (LABA + LAMA)				
Vilanterol + umeclidinium	25 mg+6 2.55 mg/inhalation	Dry powder	qid	Anora Ellipta®[d]
Leukotriene modulators				
Zafirlukast	10 and 20 mg tabs	Oral	bid	Accolate®[c]
Zafirlukast	10 and 20 mg tabs	Oral	bid	Various generics[c]
Montelukast sodium	10 mg tabs	Oral	qd	Singulair®[c]
Montelukast sodium	10 mg tabs	Oral	qd	Various generics[c]
Montelukast sodium	4 and 5 mg chewable tabs	Oral	qd	Singulair®[c]
Montelukast sodium	4 and 5 mg chewable tabs	Oral	qd	Various generics[c]
Montelukast sodium	4 mg/packet granules	Oral	qd	Singulair®[c]
Montelukast sodium	4 mg/packet granules	Oral	qd	Various generics[c]
Zileuton	600 mg tabs	Oral	qid	Zyflo®[c]
Zileuton	600 mg ext tabs	Oral	bid	Zyflo CR®[c]

Table 2 (continued)

Drug	Dose (base equivalent)[a]	Route	Frequency	Comments
Corticosteroids				
Beclomethasone diproprionate	0.4 and 0.8 mg/inhalation	MDI	bid	QVAR HFA®[c]
Budesonide	3 mg tabs	Oral	qd	Entocort EC®[e]
Budesonide	3 mg tabs	Oral	qd	Various generics[e]
Budesonide	0.25, 0.5, and 1 mg/2 ml	Inhalation/neb	bid	Pulmicort Respules®[c]
Budesonide	0.16 and 0.32 mg/inhalation	Dry powder	bid	Pulmicort Flexhaler®[c]
Budesonide	0.25, 0.5, and 1 mg/2 ml	Inhalation/neb	bid	Various generics[c]
Ciclesonide	0.08 and 0.16 mg/inhalation	MDI	bid	Alvesco HFA®[c]
Dexamethasone	0.5, 0.75, 1, 1.5, 2, 4, and 6 mg tabs oral	Oral	qd and bid	Various generics
Dexamethasone	0.5 mg/5 ml elixir	Oral	qd and bid	Various generics
Dexamethasone	4 and 10 mg/ml	Injection	qd and bid	Various generics
Fluticasone propionate	0.05, 0.1, and 0.25 mg/inhalation	Dry powder	bid	Flovent Diskus®[c]
Fluticasone propionate	044, 0.11, and 0.22 mg/inhalation MDI	MDI	bid	Flovent HFA®[c]
Mometasone furoate	0.11 and 0.22 mg/inhalation	Dry powder	qd and bid	Asmanex Twister®[c]
Methylprednisolone sodium succinate	40, 125, and 500 mg	Injection		Solu-Medrol®[c]
Methylprednisolone sodium succinate	1 and 2 g/vial	Injection	qd	Various generics[c]
Methylprednisolone acetate	40 and 125 mg/vial	Injection	qd	Various generics[c]
Methylprednisolone	20, 40, and 80 mg/ml	Injection	qd	Depo-Medrol®[c]
Methylprednisolone	40 and 80 mg/ml	Injection	qd	Various generics[c]
Methylprednisolone acetate	4, 8, 16, and 32 mg tabs	Oral	qd and bid	Medrol®[c]
Methylprednisolone acetate	4, 8, 16, and 32 mg tabs	Oral	qd and bid	Various generics[c]
Prednisone	1, 2.5, 5, 10, 20, and 50 mg tabs oral	Oral	qd and bid	Various generics[c]
Prednisone	1 mg/ml solution	Oral	qd and bid	Various generics[c]
Combination bronchodilator (LABA) + corticosteroid (ICS)				
Budesonide + formoterol fumarate	0.08+0.0045 and 0.16+0.0045 mg/inhal	MDI	bid	Symbicort®[c, d]
Fluticasone propionate + salmeterol xinaforate	0.1+0.05, 0.25+0.05, and 0.5+0.05 mg/inhal	Dry powder	bid	Advair Diskus®[c, d]
Fluticasone + salmeterol xinaforate	0.045+0.02, 0.115+0.02, and 0.5+0.02 mg/inhal	MDI	bid	Advair HFA®[c]
Fluticasone furoate + vilanterol trifenatate	0.1+0.025 mg/inhal	Dry powder	qd	Breo Ellipta®[c]
Mometasone furoate a + formoterol fumarate	0.1+0.005 and 0.2+0.005 mg/inhal	MDI	bid	Dulera®[c]
Methylxanthines				
Aminophylline	100 mg tabs	Oral	tid and qid	Various generics[c, d]
Aminophylline	25 mg/ml	Injection	Constant infusion	Various generics[c, d]
Theophylline	300, 400, 450, and 600 mg ext tabs oral	Oral	bid	Various generics[c, d]
Theophylline	80 mg/15 ml	Oral	tid and qid	Elixophyllin®[c, d]
Theophylline	100, 200, 300, and 400 mg ext caps oral	Oral	qd and bid	Theo-24®[c, d]
Theophylline	100, 200, and 300 mg ext tabs oral	Oral	bid	Theochron®[c, d]
Theophylline	125 and 250 mg tabs	Oral	tid and qid	Theolair®[c, d]
Theophylline in 5 % dextrose	4 mg/ml and 70, 80, 160, 200, 320, and 400 mg/100 ml	Injection	Constant infusion	Various generics[c, d]

COPD chronic obstructive pulmonary disease, *Neb* nebulizer, *HFA* hydrofluoralkane, *tabs* tablets, *ext tabs* extended-release tablets, *ext caps* extended-release capsules, *MDI* metered-dose inhaler, *SDM* spring-driven mist inhaler, *inhal* inhalations, *prn* as needed up to X, *qXH* every "X" hours, *qd* once a day, *bid* twice a day, *tid* three times a day, *qid* four times a day, *cont* continuous, *max* maximum dose

[a] Dose or drug concentration if variable dose injections are described

[b] Reversible airway obstruction (FDA indication)

[c] Asthma (FDA indication)

[d] Chronic obstructive pulmonary disease (FDA indication)

[e] Crohn's disease no airway indications-reduced systemic absorption (FDA indication)

dosing with the newest ones (indacaterol, olodaterol, and vilanterol) are seen (Table 2).

Small increases in asthma and all-cause mortality rates with the use of LABAs in several post-marketing studies including the Salmeterol Multicenter Asthma Research Trial (SMART) which evaluated 26,355 patients treated with the LABA salmeterol or placebo added to their usual asthma care have been reported [34, 35]. Subgroup analysis in the SMART suggested this risk was fourfold greater in African Americans compared to Caucasian subjects [34]. As a result of several meta-analyses, the FDA placed a "black box warning" on LABAs contraindicating their use as monotherapy yet continuing their use with an ICS in persistent asthma patients.

Short-Acting Muscarinic Antagonist (SAMA)

Both muscarinic receptor 2 (M2) and muscarinic receptor 3 (M3) are expressed in bronchial and tracheal smooth muscle. The role of the M2 receptor is unclear but the M3 receptor when stimulated by the parasympathetic neurotransmitter acetylcholine inhibits airway smooth muscle relaxation induced by beta$_2$ agonists [36]. Stimulation of the M3 receptor also causes submucosal glands to release mucus and may play a role in airway remodeling and inflammation. Inflammation by itself can amplify cholinergic tone [36]. Ipratropium is a SAMA with airway effects of about 6 h, while the longer acting agents (tiotropium, umeclidinium, and aclidinium) slowly dissociate from and antagonize M3 receptors lasting at least 12–24 h.

Currently, SAMAs alone or in combination with a SABA are not FDA-approved for AEA. Several ED AEA treatment guidelines and reviews include the use of inhaled SAMAs [3, 14]. The use of SAMAs alone compared to either SABAs alone or SAMAs + SABAs was less efficacious in treating AEA [37]. A meta-analysis of AEA in children found a significant improvement in lung function 60 min after a single dose of a SAMA combined with SABAs but no change in hospital admission rates [38]. In contrast, multiple doses of SAMAs combined with SABAs resulted in significant improvement in lung function and reduced hospital admissions. A meta-analysis of 32 randomized controlled trials in the ED of 3,611 patients showed significant reductions in hospital admissions in both adults and children treated with multiple doses of SAMAs + SABAs compared to SABAs alone in acute of moderate to severe AEA. The use of combined treatment of SAMA + SABA produces significant improvement in lung function compared to a SABA alone [39]. The use of combined multiple dose of a SABA + SAMA has been called the "first-line" therapy for severe AEA in the ED by some authors [40].

Long-Acting Muscarinic Antagonists (LAMAs)

The use of LAMAs in the treatment of AEA is not recommended in asthma guidelines and nor are they FDA-approved for asthma (Table 2). Recent studies have suggested an emerging role for LAMAs in difficult-to-control asthma patients, and they should be considered at hospital or ED discharge of a patient with refractory or difficult to control asthma or ACOS [10, 36, 41, 42]. Another group that may benefit from LAMA therapy includes patients with the *ADB$_2$R-B16-Arg/Arg* genotype who are poorly controlled on ICS. When these patients were randomized to receive either a LAMA or LABA, the LAMA was found to be non-inferior to the LABA [43]. These patients represent 10–12 % of white and 20–25 % of African American asthmatic subjects and may be less responsive to or worsen with LABAs [43]. Since the genotypes of patients are not routinely known in the clinic or ED, LAMA initiation at clinic, hospital, or ED discharge should be considered for difficult-to-control patients, particularly African American patients.

Dry mouth, dry respiratory secretions, cough, urinary retention, dilated pupils, blurred vision (if put into eyes), and increases in intraocular pressures in patients with glaucoma are major SAMA/LAMA side effects.

Corticosteroids

The preferred initial controller drugs in persistent asthma are ICS and systemic corticosteroids (SC) in AEA [3, 14]. The NAEPP Expert Panel 3 guidelines and various reviews have focused on the importance of ICS therapy in treating persistent asthma patients [3, 44].

Corticosteroids have many cell- and tissue-specific anti-inflammatory effects including binding to the cytoplasmic glucocorticoid receptor (GR) [45]. Corticosteroid interaction with the GR induces conformational changes that allow activated GR to bind to responsive DNA sequences promoting the synthesis of anti-inflammatory proteins and inhibiting the transcription of many pro-inflammatory cytokines [46]. Secondary effects include reducing T lymphocytes, mast cells, eosinophils, and dendritic cells [46]. More complex and poorly understood effects of corticosteroids are needed to explain the entirety of the corticosteroid manifestations [45, 47, 48].

The use of corticosteroids in the treatment of AEA is well-established [49]. Patients presenting to a clinic or an ED with AEA are frequently treated with oral or intravenous (iv) corticosteroids. Current guidelines suggest a 5–10-day post-ED course of oral corticosteroids should be given [50]. When SCs are given to children with AEA, earlier discharges and fewer relapses were seen [51]. SC given within 75 min of triage decreased hospital admission rates and the length of

treatment in a prospective observational study of moderate and severe AEA in children [52]. Hospitalized patients with severe AEA treated with high-dose or low-dose SC did not have differences in outcomes [53]. Several trials have specifically shown that oral and iv SC produce similar clinical outcomes in AEA that require hospitalizations [54–56]. Studies in both children and adults treated and discharged from an ED or clinic comparing intramuscular corticosteroids to short courses of oral prednisone or methylprednisolone report that the intramuscular dose was as effective as the short course of oral corticosteroids in reducing the relapse rate of AEA [57–60]. Supporting the importance of early therapy, a separate systematic review of the use of SC within the first hour of ED presentation demonstrates significant reduction in the need for hospitalization in AEA [61].

Using ICS to treat AEA is less common but a meta-analysis has suggested patients initially treated with ICS therapy can reduce hospital admissions when it is paired with SC [62]. ED-discharged patients on tapering doses of oral corticosteroids were randomized to placebo or the addition of ICS therapy [63]. Those patients receiving ICS had statistically significant reductions in relapse rates and improved symptom scores compared to placebo. A recent meta-analysis failed to confirm that the use of ICS after ED discharge for AEA provided additional benefit when paired with systemic corticosteroids [62]. Suggesting the importance of dose, a subgroup analysis of high-dose ICS at the time of discharge from the ED was suggestive of improved clinical outcomes [62]. The majority of children discharged from Canadian EDs left on only an inhaled SABA and not a combination of a SABA and oral steroid or ICS [64]. Patients with frequent ED visits or a history of difficult to control asthma with poor outpatient follow-up would be excellent candidates for starting ICS at discharge. Insufficient data exist to suggest ICS therapy alone can be used instead of systemic corticosteroids in treating AEA.

Adverse effects with corticosteroids are related to the dose, their potency, the route, and the total time of corticosteroid exposure. The use of ICS is associated with cough, dysphonia, and oral thrush. Impaired growth in children, adrenal axis suppression, immunosuppression, decreased bone mineral density, avascular necrosis, skin thinning, glucose intolerance, bruising, and cataracts are also reported [65, 66]. Early initiation of high-dose ICS appears to be effective for the treatment of episodic viral wheeze of childhood [67–69]. In contrast, chronic use of ICS in asthma treatment has been associated with small increases in pneumonia and mycobacterium [70, 71]. The suppression of cortisol was dose-dependent when six ICSs were tested in 156 naive asthma subjects [72]. A new corticosteroid, ciclesonide, is a "pro-drug" with unique pharmacokinetics and once-daily dosing. It was hoped to reduce systemic toxicities, but this has not been confirmed [66, 73].

Leukotriene Modulators

Leukotriene receptor antagonists (LTRA) and the 5-lipoxygenase inhibitor zileuton are alternative chronic therapies to ICSs for adults and children with persistent asthma. LTRA (montelukast, pranlukast, and zafirlukast) block leukotriene D_4 from interacting with cysteinyl leukotriene receptors on airway smooth muscle reducing bronchospasm and airway hyperresponsiveness [74]. The inhibition of the 5-lipooxyenase enzyme by zileuton blocks the formation of cytosol leukotrienes and other products associated with bronchoconstriction [74].

Intravenous montelukast has been studied in AEA with improvement in forced expiratory volume in 1 s (FEV_1) documented [75]. The clinical data has not been strong enough to gain FDA approval in the USA. Oral LTRA are generally not included in the treatment guidelines of AEA [3, 14, 75]. A recent randomized, double-blind, placebo-controlled trial of oral montelukast in adults with AEA failed to show benefit [76]. This result is consistent with a systematic review of eight trials of LTRA which also did not support their oral use in AEA. Because of early positive results, a call for more clinical trials to better understand if there is a potential role for iv montelukast in acute severe asthma patients has been made [77]. Limited data exists regarding the other LTRA and the 5-lipoxygenase inhibitor zileuton in the AEA. Although a logical choice, no data exists about starting these agents at the time of discharge from the hospital or the ED after successful treatment of an AEA.

Adverse effects with montelukast and zafirlukast have been limited. Acute adverse effects are lacking, and chronic effects are limited to rare cases of Churg-Strauss vasculitis [3, 78]. Hepatitis has been reported with chronic zafirlukast which resulted in hepatic failure requiring liver transplant and death. The chronic use of zileuton use has also resulted in elevated liver enzymes in about 5 % of asthma patients [79, 80].

Methylxanthines

Available methylxanthines (Table 2) include theophylline and aminophylline (a 2:1 theophylline/ethylenediamine compound). A recent review of theophylline notes its limited use is as an "add-on" therapy in patients not well controlled on ICS with or without LABAs [81]. Current guidelines for treating AEA do not recommend routine use of iv aminophylline even though it once was "standard treatment" in the ED [3, 14, 75].

The limited bronchodilator effect of theophylline is through inhibition of phosphodiesterase (PDE) 3. A limited anti-inflammatory effect of theophylline may be from its inhibition of PDE4 and histone deacetylase-2 activation which turns off activated inflammatory genes and can reverse corticosteroid

resistance seen in some patients [81, 82]. Improved diaphragm contractility and mucociliary clearance occurs with theophylline [3].

In a randomized, double-blind, placebo-controlled trial of 163 children with AEA unresponsive to three nebulized SABA treatments, aminophylline resulted in greater airflow improvement at 6 h, and fewer patients required intubation and mechanical ventilation than placebo [83]. In contrast, children between 2 and 5 years of age with AEA in the ED randomized to aminophylline failed to show any change in the number of required SABA treatments, duration of oxygen treatment, and length of hospital stay [84]. Adding theophylline to continuous albuterol nebulization and iv corticosteroids in children in status asthmaticus was as effective as adding terbutaline and more cost-effective [85]. Despite these results, a meta-analysis evaluated 13 trials in severe AEA and failed to show a difference between the aminophylline-treated group and the control groups despite widespread use of it at the time that most of the studies were done [86]. Another more recent systematic review included 15 trials of AEA and also found no statistically significant improvement with aminophylline on airflow outcomes compared to SABA therapy. Significant increases in palpitations and arrhythmias but not a reduction in hospital admissions were found with aminophylline treatments [87].

The limited role of theophylline in the treatment of AEA is because of both the lack of supportive efficacy data and significant adverse effects associated with its use. These include headaches, nausea, vomiting, gastrointestinal distress, cardiac arrhythmias, and seizures [81]. The multiple drug–drug interactions generated when theophylline is used along with the need for a monitoring blood levels have almost eliminated its use in the ED for AEA.

Magnesium Sulfate

The use of iv magnesium is not addressed in several guidelines and reviews on the treatment of AEA while others support its use [14, 16, 17, 75, 88]. Possible mechanisms to explain the bronchial smooth muscle relaxation seen with magnesium include blocking calcium influx into the cytosol by and its release from the endoplasmic reticulum and activating sodium–calcium pumps [89, 90]. Further, magnesium can block the interaction between calcium and myosin leading to muscle cell relaxation. T cell stabilization, inhibition of mast cell degranulation, blockade of histamine release, inhibition of inflammatory mediators, and acetylcholine release from cholinergic nerves all have been reported with magnesium. Increases in B_2R agonist affinity and stimulation of both nitric oxide and modulation prostacyclin synthesis by magnesium may lead to bronchodilation.

The use of iv magnesium given during the first hour of presentation in a recent randomized study of 143 children with AEA significantly reduced the need for mechanical ventilation (33 vs. 5 %, P=0.001) [91]. Improved outcomes in adults and children with AEA treated with iv magnesium are reported in several systematic reviews and meta-analyses [89, 90, 92]. Combining iv magnesium with inhaled SABAs and systemic corticosteroids markedly improved spirometry and reduced rates of hospitalization in children and improved spirometry in adults [90]. Intravenous magnesium should be considered early in the ED treatment of severe AEA in the ED in patients not clinically responding to aggressive bronchodilator therapy and systemic steroids within the first hour of presentation.

Nebulized magnesium sulfate was concluded to be better than placebo as an acute bronchodilator in AEA [88]. When nebulized magnesium sulfate is added to a nebulized SABA, improved pulmonary function and reduced hospital admissions are seen [93]. In contrast, another meta-analysis found only weak evidence for improvement in pulmonary function and reduced hospital admission rates with nebulized magnesium in adults but not in children [92]. A recent Cochrane Systematic Review noted no evidence exists that inhaled magnesium can substitute for SABAs or consistently adds to inhaled SABAs when combined [94]. Adding to the confusion, another recent meta-analysis found nebulized magnesium combined with a SABA compared to a nebulized SABA alone improved pulmonary function and reduced hospital admissions in adult patients with AEA [90]. Obviously, further study with both inhaled magnesium and the current recommended bronchodilators (SABAs + SAMAs) is needed to better understand if there is a role for nebulized magnesium in the treatment of AEA [94, 95].

Magnesium adverse events are infrequent in acute iv use with minor side effects including flushing, iv site pain, and fatigue [88]. High-dose iv magnesium and prolonged dosing particularly in patients with abnormal renal function increase the risk for the more serious magnesium side effects such as hypotension, hyperreflexia, arrhythmia, and respiratory depression.

Heliox

Heliox, a combination of helium and oxygen gas with a long history in airway diseases, was first evaluated in asthma in the 1930s [96]. Its low density and viscosity give helium favorable characteristics in the laminar and turbulent flow common in asthma patients. Technical aspects of using Heliox must be addressed and have improved with the commercial availability of regulators, flow meters, and devices that are designed and calculated for the commonly available helium and oxygen mixed concentrations of 80:20 and 70:30 [97]. Several FDA-approved bronchodilator nebulization devices are now available for use with Heliox [98]. When Heliox is used to drive bronchodilator nebulization, deeper lung delivery of the agent

is seen [98]. Improved FEV_1 is seen using Heliox-driven bronchodilator nebulization compared to using pure oxygen-driven systems [99, 100]. In children (ages 2–21 years) using Heliox-powered albuterol, nebulization failed to demonstrate shorter hospitalizations in moderate-to-severe AEA compared to oxygen-driven albuterol nebulization [101]. A systematic review evaluated the use of Heliox-driven nebulizers and noted improved air flow measures in patients compared to those getting oxygen-driven nebulizers but failed to show improved rates of recovery [102]. Although a recent review concluded the role of Heliox in the management of acute asthma is still "unclear," [14] the majority of data supports using Heliox-driven albuterol nebulization for severe AEA in patients remaining critical after 1 h of intensive conventional therapy [3].

When Heliox (60:40 or 70:30 concentrations) inhalation was used, instead of oxygen, in adult patients presenting with AEA, both arterial carbon dioxide and pH determinations were rapidly improved [103]. A randomized controlled trial of Heliox (70:30) compared to 30 % oxygen in the ED with AEA patients resulted in both statistically improved peak expiratory flow rates and symptoms [104]. A systematic review of the use of Heliox during the first hour of acute asthma treatment concluded mild-to-moderate benefits were seen in peak expiratory flow rates and dyspnea scores [105]. A seven trial systematic review of adults and children treated with Heliox confirmed an improvement in pulmonary function in the subgroup of patients with the most severe AEA but failed to show overall clinical improvement [106]. If Heliox is to be used, it is most likely to be effective in the first few hours in patients refractory to initial aggressive bronchodilator and steroid therapy.

The greatest risk of Heliox therapy is when it is used in a "jury-rigged device" by an incompletely trained provider [97]. The use of equipment to monitor and devices not approved for Heliox creates the risk of providing low oxygen concentrations, generating excessive tidal volumes on a ventilator, and delivering too little or too much of the bronchodilators.

Emerging Agents

The prevention of AEA events is the focus of most new asthma agents. The relative success of the biological agent omalizumab in refractory IgE-associated chronic asthma has generated wide interest in other potential biologic treatments [107]. Several other biological inflammatory modulators include IgG antibodies to IL-5, IL-13, IL-4, IL-9, and IL-17, and tumor necrosis factor alpha is being evaluated for long-term control of asthma [107]. Two chronic non-biological approaches, using azithromycin or using statin therapy to date, have not been shown to reduce the rate of AEA [108, 109]. Adults with severe AEA failed to show any advantage when recombinant human DNAse was nebulized and with standard bronchodilators [110].

Low-dose iv ketamine in two randomized trials in AEA failed to demonstrate increased bronchodilator effect compared to standard therapy [111, 112]. Oral ketamine has also failed to show a significant benefit in non-intubated children with severe AEA [113]. High-dose ketamine has been advocated in case reports for AEA patients on mechanical ventilation [114]. A review of the use of oral ketamine in AEA found only one qualifying randomized study found. This trial failed to find significant benefit in non-intubated children [113]. Because the currently available inhaled and parenteral agents are generally very effective, relatively inexpensive and reasonably safe in controlling the vast majority of patients with AEA, new drug development for the acute treatment of AEA has been limited [115].

Conclusion

Current pharmacological review of the treatment options for AEA is summarized in Fig. 1. After a trial of inhaled SABA or combined inhaled SABA/SAMA treatment, patients who remain symptomatic will require frequent or constant dosing of these agents. Systemic corticosteroids remain the main acute

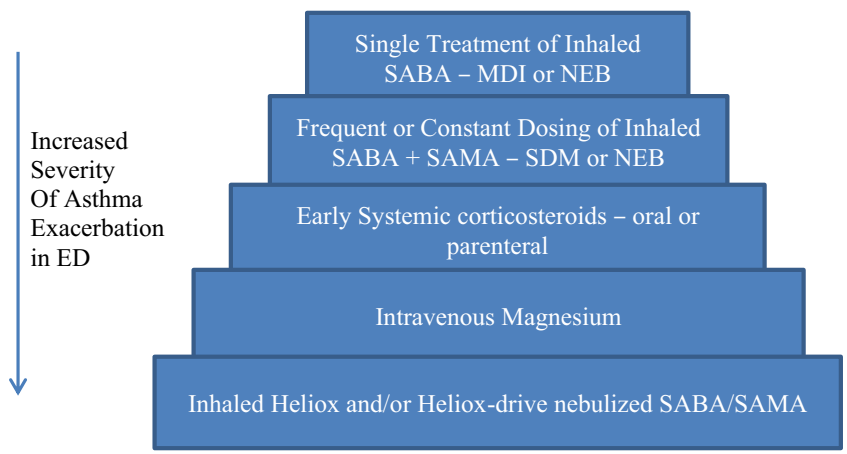

Fig. 1 Pharmacological interventions in the treatment of asthma exacerbations in the clinic or emergency department (ED). *SABA* long-acting beta$_2$ agonists (levalbuterol); *MDI* metered-dose inhaler with spacers; *Neb* nebulized inhaled treatment; *SAMA* short-acting muscarinic antagonists (ipratropium); *SDM* spring-driven mist device; *Heliox* helium/oxygen mixture at ratio of 20:80 or 30:70 ratio

anti-inflammatory treatment for AEA treated in the ED. The use of iv magnesium, inhaled Heliox, and Heliox-driven nebulizers appears to be an effective adjunctive approach for severe AEA if used within the first few hours. Theophylline, ICS, leukotriene modifiers, and LABA and LAMA inhalers currently do not play a major role in treating AEA but may be important to initiate at the time of clinic, hospital, or ED discharge.

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