Management of Asthma Exacerbations in the Emergency Department

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Asthma exacerbations occur across a wide spectrum of chronic severity; they contribute to millions of emergency department (ED) visits in both children and adults every year. Management of asthma exacerbations is an important part of the continuum of asthma care. The best strategy for ED management of an asthma exacerbation is early recognition and intervention, continuous monitoring, appropriate disposition, and, once improved, multifaceted transitional care that optimizes subacute and chronic asthma management after ED discharge. This article concisely reviews ED evaluation, treatment, disposition, and postdischarge care for patients with asthma exacerbations, based on high-quality evidence (eg, systematic reviews from the Cochrane Collaboration) and current international guidelines (eg, the National Asthma Education and Prevention Program Expert Panel Report 3, Global Initiative for Asthma, and Australian guidelines). Special populations (young children, pregnant women, and the elderly) also are addressed. Despite advances in asthma science, there remain many important evidence gaps in managing ED patients with asthma exacerbation. This article summarizes several of these controversial areas and challenges that merit further investigation. **(J Allergy Clin Immunol Pract 2021;9:2599-610)**

Key words: *Review; Asthma exacerbation; Emergency department; Diagnosis; Treatment; Disposition; Children; Adults*

INTRODUCTION

Asthma is defined as a chronic inflammatory disorder associated with variable airflow obstruction and bronchial hyperresponsiveness.[1] Asthma exacerbations refer to severe episodes of worsening disease, characterized by cough, shortness of breath, wheeze, and chest tightness. They occur across the spectrum of chronic severity (from intermittent asthma to severe persistent asthma) and significantly contribute to the public health burden of asthma.

In the United States alone, asthma exacerbations led to at least 1.7 million emergency department (ED) visits and 200,000 hospitalizations in 2016.[2] Asthma also costs US society an estimated direct cost of $50 billion.[3] Asthma exacerbations cared for in an ED cost approximately 5 times that of an office-based visit.[4] In this context, the US government has identified improving asthma care, reducing asthma-related ED visits, and reducing hospitalizations as key health policy objectives.[5]

ED EVALUATION

An asthma exacerbation is diagnosed by a combination of symptoms, such as an episode of progressive dyspnea, wheezing, chest tightness, and cough. Although many patients recognize worsening symptoms, others have difficulty perceiving decreased airflow.[6] For the latter group of patients, an objective decline in peak expiratory flow (PEF) or FEV_1 may be the first sign of an asthma exacerbation.[7] Objective measurement of pulmonary function, albeit often neglected,[8,9] is therefore an important part of the ED evaluation. Although measurements of FEV_1 are preferred, serial PEF measurements help ED providers estimate the severity of airflow limitation, guiding ED management and enabling the monitoring of response to therapy. International guidelines recommend their use unless patients are in severe respiratory distress or are young children.[7,10,11]

Although the diagnosis of asthma is often straightforward, there are a number of other conditions that should be considered (Table I), particularly if the patient is not responding to treatment as expected. Comorbid conditions in elderly patients can also make the diagnosis more challenging. A major differential diagnosis in older adults is chronic obstructive pulmonary disease (COPD). In both asthma and COPD, pulmonary function tests show evidence of airflow limitation, although this may not be

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Abbreviations used
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
EPR3- Expert Panel Report 3
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
PEEP- Positive end-expiratory pressure
PEF- Peak expiratory flow
pMDI- Pressurized metered-dose inhaler
RCT- Randomized controlled trial
SABA- Short-acting β_2-agonist

reversible in COPD. Moreover, patients with COPD with a diminished diffusion capacity may present with hypoxemia. In the emergency setting, it may be difficult to rapidly distinguish these 2 diseases; they also may coexist. Cardiac etiologies, such as heart failure, can also mimic an asthma exacerbation. The diagnosis should be considered in patients with a history of ischemic heart disease, clinical evidence of volume overload, or other stigmata of heart failure. Vocal cord dysfunction may cause symptoms of severe dyspnea and may be difficult to differentiate from asthma; these 2 conditions may also coexist.[12] It is more common in younger patients. The recently developed Pittsburgh Vocal Cord Dysfunction Index—which uses throat tightness, dysphonia, absence of wheezing, and presence of odors as a symptom trigger—showed good sensitivity (0.83) and specificity (0.95) in distinguishing vocal cord dysfunction from asthma, and was validated in a non-ED independent sample.[13]

Asthma is a common childhood illness, and it is reasonable to commence therapy in a child with typical signs and symptoms. However, if a child does not respond to standard asthma treatment, they should be carefully evaluated for other diagnoses (Table I). Unilateral wheeze and onset of respiratory distress after a choking spell suggests foreign body aspiration. It is also important to distinguish between signs of upper airway obstruction presenting with stridor (such as croup) from signs of lower respiratory tract illness (eg, crackles and wheeze).

ED TREATMENT

General approaches

The primary treatment objectives of asthma exacerbation in the ED are (1) correction of hypoxemia, (2) reversal of airflow limitation, and (3) reduction of future recurrences.[7] Reversal of airflow limitation is achieved by the administration of inhaled short-acting β_2-agnosists (SABAs) and early use of systemic corticosteroids. In addition, adjunct pharmacologic agents—for example, inhaled anticholinergics and intravenous magnesium sulfate—may be beneficial in severe exacerbations and impending respiratory failure. Nonpharmacologic options include noninvasive and invasive mechanical ventilation. We briefly review the evidence for these treatment options in the ED.

International guidelines[10,11]—such as the National Asthma Education and Prevention Program Expert Panel Report 3 (EPR3) guidelines[7]—have offered useful management algorithms for patients with asthma exacerbation in the ED setting based on the acute severity (Figure 1). After obtaining a brief history, performing physical examination, and measuring pulse oximetry, objective lung function assessment is recommended. For older children and adults, the guidelines use the percent of predicted or personal best PEF (or FEV_1) thresholds at 70% for mild exacerbations and at 40% for severe exacerbations. The 70% threshold for mild exacerbations is a goal for safe discharge from the ED. The 40% threshold for severe exacerbations is clinically relevant because it is at the level below which adjunctive treatment options are most beneficial. That said, we acknowledge that these thresholds are based largely on local consensus. The Global Initiative for Asthma (GINA) guidelines use different thresholds (eg, PEF >60% predicted or personal best as a criterion for ED discharge).[10] The Australian guidelines place less emphasis on objective measures of pulmonary function.[11,14] To assess the response to management, ED providers should perform serial monitoring and reassessment (eg, subjective response, physical findings, PEF, and pulse oximetry) immediately after the initial dose of SABA in patients with severe exacerbation and after the doses of SABA in all patients.[7]

Laboratory testing and chest radiographs are not necessary unless the patient is critically unwell. Routine chest X-rays in uncomplicated cases are rarely helpful,[15] and are not recommended in children with a first episode of wheeze.[16]

Pharmacologic treatment

Short-acting β_2-agonists. The cornerstone of bronchodilator treatment is inhaled SABA (eg, albuterol [salbutamol] and levalbuterol), which should be used in all ED patients with asthma exacerbation.[7] SABAs have a rapid onset of action (3-5 minutes) and work through β_2 adrenergic receptors to relax airway smooth muscle and to stabilize mast cells. High doses may cause tachycardia, tremor, anxiety, and lactic acidosis (even without hypoxemia).[17] Levalbuterol—which contains only the active isomer of albuterol—has been marketed as a medication with fewer adverse effects than albuterol; however, a meta-analysis demonstrated that the observed differences do not have meaningful clinical significance.[18]

SABAs are delivered either with a pressurized metered-dose inhaler (pMDI) with the use of a valved holding chamber (4-8 puffs [90 μg/puff] every 20 minutes for the first hour) or with a nebulizer (2.5-5.0 mg albuterol every 20 minutes for the first hour).[19] A Cochrane systematic review of 39 clinical trials involving both children and adults in the ED[20] did not show significant differences in PEF, FEV_1, or hospitalization rate between pMDI and nebulizer administration of SABA. Children treated using a pMDI with valved holding chamber had a shorter ED length of stay and fewer adverse events than those treated with nebulized SABA. In the ED, nebulized administration of SABA may be preferred for patients because of the simplicity of delivery,[21] particularly in patients who are unable to cooperate in using pMDIs because of their age, mental status, and severity of the exacerbation. However, use of nebulizers may reinforce the need for a relatively costly hospital-based treatment. Nebulization may also disseminate aerosols, potentially contributing to spread of respiratory viral infections,[22] an important consideration during the coronavirus disease 2019 pandemic. Unless a patient is too sick to use it effectively, patients with acute exacerbations of asthma should be treated with a pMDI and a valved holding chamber.

For patients with severe exacerbations, research has shown potential advantages of continuous over intermittent administration of SABAs. In a systematic review of 8 randomized controlled trials (RCTs) involving both children and adults,[23] the use of continuous nebulization (defined as nebulization of at least

TABLE I. Differential diagnosis of asthma exacerbation in the ED

Etiology	Children	Adults
Upper airway	Bacterial tracheitis Croup Laryngotracheomalacia Vocal cord dysfunction (inducible laryngeal dysfunction)	Laryngeal neoplasm Vocal cord dysfunction (inducible laryngeal dysfunction)
Pulmonary	Bronchiolitis Cystic fibrosis Foreign body Pneumonia Tracheal stenosis Virus-induced wheezing Noncardiac pulmonary edema Pulmonary sequestration Congenital lobar emphysema	Acute exacerbation of COPD Bronchiectasis Excessive dynamic airway collapse Recurrent aspirations Pneumonia Pulmonary embolism/infarction Tumors Noncardiac pulmonary edema
Cardiac	Congenital heart disease	Heart failure
Gastrointestinal	Gastroesophageal reflux disease	Gastroesophageal reflux disease
Allergic	Anaphylaxis	Allergic bronchopulmonary aspergillosis Anaphylaxis
Others	Swallowing dysfunction Vascular ring/sling	Churg-Strauss syndrome

2.5-5 mg of albuterol every 15 minutes or >4 nebulizations per hour) improved pulmonary function and decreased hospitalization risk when compared with intermittent nebulization. Some guidelines suggest its use in patients with severe exacerbation.[22] When continuous nebulization is not used, 3 treatments of SABA spaced every 20 to 30 minutes may be provided efficaciously and safely as the initial therapy.[7] The frequency and dose of SABAs should be titrated according to symptoms, airflow limitation, and adverse effects.[7]

We do not recommend the use of oral SABAs because of concerns regarding low and variable efficacy, narrow therapeutic index, and high rates of adverse effects.[24]

Inhaled anticholinergics. Several studies have shown that adding inhaled anticholinergics (typically ipratropium bromide) to SABA treatment in the ED provides additional bronchodilation, with a reduced risk of hospitalization, particularly in patients with severe airflow limitation.[7] In children, the evidence is robust. In a Cochrane systematic review of 24 trials—mainly preschool-age and school-age children with moderate to severe exacerbations—a combination of inhaled anticholinergics and SABA significantly decreased hospitalization risk[25] and led to a greater improvement in pulmonary function and fewer adverse events (eg, tremor and nausea).[25] Likewise, in a meta-analysis of 23 studies involving ED adults with asthma exacerbation,[26] the addition of ipratropium bromide significantly reduced hospitalization risk compared with SABA alone. Notably, this effect was only observed in patients with severe exacerbations. Combined therapy also improved PEF and FEV_1 and lowered the risk of ED revisits. Accordingly, the current evidence supports the use of combined therapy for patients with moderate to severe exacerbation.

Systemic corticosteroids. The early use of systemic corticosteroids (eg, within 1 hour of ED arrival) is a critical component of ED treatment,[7,10,11] with beneficial effects on airflow limitation caused by inflammation, edema, and secretions. In a meta-analysis of 12 clinical trials of ED patients with asthma exacerbation, early administration of systemic corticosteroids significantly decreased the hospitalization risk, with a greater effect in patients with severe exacerbation. Although the efficacy of systemic corticosteroids is well documented,[7] the optimal steroid, dose, and duration remain uncertain. A systematic review of 6 RCTs showed no between-dose differences in FEV_1, respiratory failure, or adverse effects,[27] while daily doses of oral corticosteroids equivalent to 1 to 2 mg/kg prednisolone (for 3-5 days) in children and 50 mg prednisolone (for 5-7 days) in adults are considered sufficient for most asthma exacerbations.[10] Recent research has also reported that a shorter duration of oral dexamethasone (eg, 0.6 mg/kg/d for 1-2 days in children; 12 mg/d for 1-2 days in adults) is tolerated, and just as effective as oral prednisolone in both children and adults.[28-31]

Although oral prednisone and intravenous methylprednisolone have an equivalent efficacy given the virtually complete bioavailability,[32,33] oral corticosteroids are preferred under most circumstances. Intravenous administration should be reserved for critically ill patients or those who cannot tolerate oral administration.[7,10,11]

Nonstandard therapies for severe asthma exacerbations

Although most ED patients with asthma exacerbation sufficiently respond to SABAs and systemic corticosteroids, some develop signs of worsening distress.[34] Because respiratory failure can progress rapidly and be difficult to reverse, early recognition and intensive intervention are crucial. Although uncertainties in the evidence remain,[35] international guidelines recommend the consideration of adjunct treatments for ED patients with a severe exacerbation or impending respiratory failure.[7,10,11]

Magnesium sulfate. *Intravenous* magnesium sulfate has immediate bronchodilator effects by inhibiting calcium influx into airway smooth muscle cells and anti-inflammatory effects.[36] Although its routine use does not offer incremental benefits to patients who have received SABA and systemic corticosteroids,[37] in a meta-analysis of 14 trials involving ED adults with severe

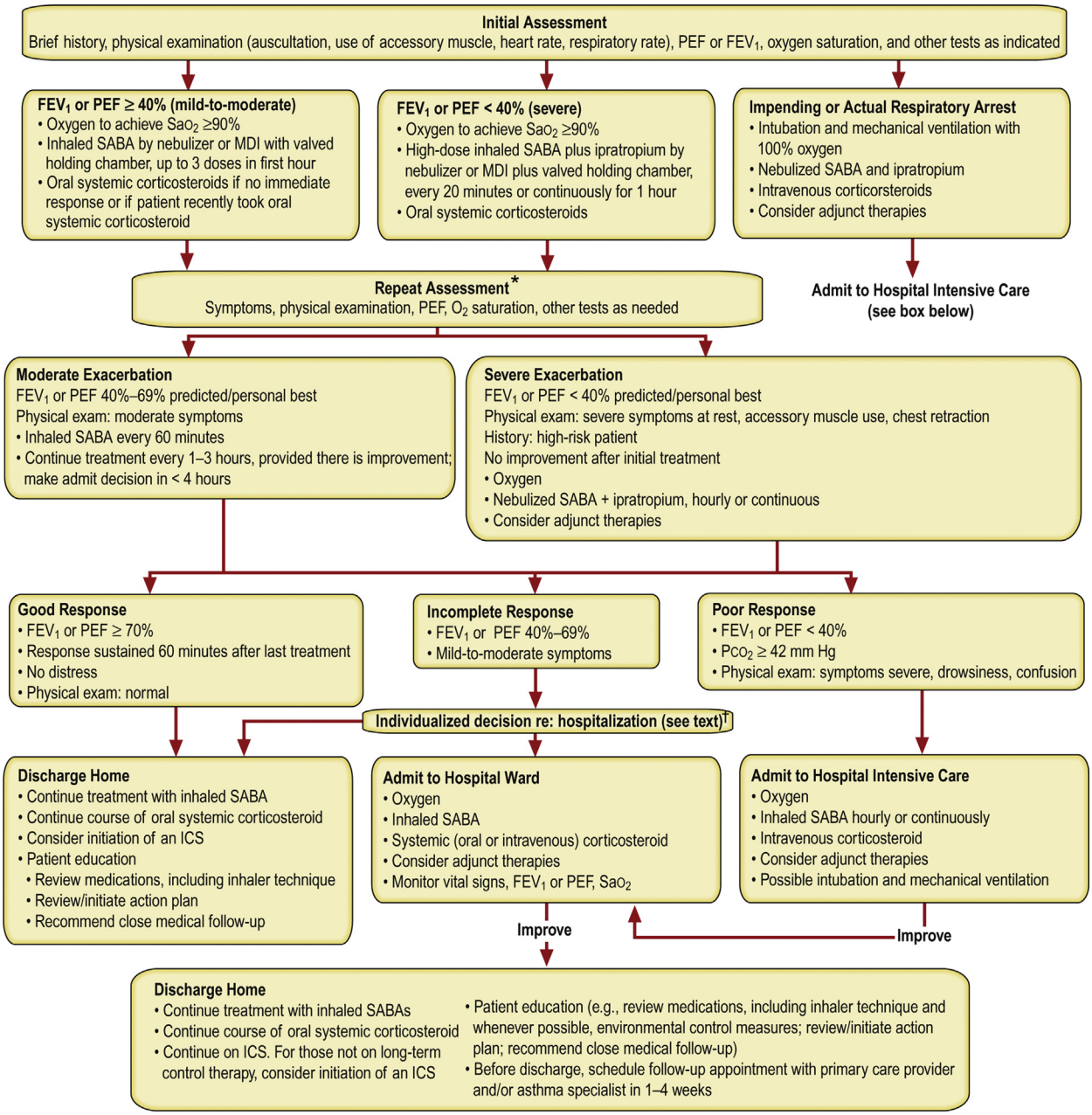


FIGURE 1. ED management of asthma exacerbations in older children and adults. *MDI*, Metered-dose inhaler; *PCO_2*, partial pressure carbon dioxide; *SaO_2*, oxygen saturation. Reproduced from Burks AW, Holgate ST, O'Hehir RE, Bacharier LB, Broide DH, Hershey GK, et al. Middleton's principles and practice. 9th ed. Elsevier Health Sciences; 2019. This figure originates from the National Asthma Education and Prevention Program.[7] *Patients who have achieved greater than or equal to 70% PEF or FEV_1 should go to the "Good Response" category. †The factors that influence individual decisions to hospitalize may be found in the text (the ED disposition section) and Table II.

asthma exacerbation, it was found that the magnesium sulfate group achieved a lower hospitalization rate and modest improvement in PEF and FEV_1.[38] A Cochrane review of intravenous magnesium in children with asthma exacerbations found low-quality evidence (a total of 115 children from 3 studies) for a reduction in hospitalization, and recommended further research, ideally using agreed core outcome measures and pragmatic markers of severity.[39] Although not all studies have reported positive results,[40-42] this agent has an excellent safety profile and is inexpensive.[38] Accordingly, the EPR3 guidelines support consideration of its use (25-75 mg/kg [maximum 2 g] in children; 2 g in adults) in patients who have life-threatening exacerbation or those who remain in the severe category despite 1 hour of intensive conventional therapy.[7]

The role of *inhaled* magnesium sulfate in the management of asthma exacerbation is inconclusive. A Cochrane systematic review of 16 RCTs involving both children and adults[43] was unable to derive definitive conclusions due to considerable

heterogeneity among studies. The addition of inhaled magnesium sulfate to SABA with or without inhaled anticholinergics did not significantly improve pulmonary function or reduce hospitalization risk. Similarly, in a large RCT (the 3Mg trial) that enrolled 1109 adult ED patients with severe exacerbation, nebulized magnesium sulfate did not improve symptoms or reduce hospitalization risk, compared with placebo.[44] Furthermore, in a recent multicenter RCT on 816 children with refractory asthma exacerbation in pediatric EDs, inhaled magnesium with albuterol did not significantly reduce the hospitalization rate.[45] Currently, there is no robust evidence that supports inhaled magnesium as a combined therapy with SABA.

Helium-oxygen mixtures (heliox). Although heliox has been used to treat patients with severe asthma exacerbation to reduce the work of breathing and improve ventilation (through reducing airway flow resistance), the evidence base is inconclusive. In a meta-analysis of 11 trials involving both children and adults, *post hoc* analysis limited to patients with severe exacerbation showed that the use of heliox significantly improved PEF.[46] Within the pediatric trials, heliox-driven β_2-agonists nebulization lowered the exacerbation severity and hospitalization risk without an increase in serious adverse effects. Yet, the meta-analysis observed significant heterogeneity among studies. Although the efficacy of heliox in ED management of asthma exacerbation remains uncertain, the EPR3 guidelines recommend a consideration of heliox-driven β_2-agonist nebulization for patients with life-threatening exacerbation and for those who remain in the severe category after 1 hour of intensive conventional therapy.[7]

High-dose inhaled corticosteroids. Inhaled corticosteroids (ICSs) are a cornerstone of treatment for persistent (chronic) asthma,[47] but their role in ED management of asthma exacerbation remains controversial. In a Cochrane systematic review of 20 trials involving both children and adults with modest heterogeneity,[48] compared with the placebo group, the ICS group achieved a small but significant improvement in PEF and FEV_1 and reduction of hospitalization risk, without significant differences in the adverse event rates. The observed effect on hospitalization risk was significant across patients with and without the concomitant use of systemic corticosteroids, whereas moderate heterogeneity was observed in those with systemic corticosteroid use. In contrast, in the secondary analysis of studies comparing ICSs alone to systemic corticosteroids, the between-study heterogeneity precluded the authors from drawing definitive conclusions. Based on current evidence, ICSs probably are not a substitute for systemic corticosteroids, and their role as an adjunct is unclear.

Leukotriene modifiers. Leukotriene modifiers (eg, montelukast and zafirlukast) act through downregulating the downstream effects of leukotrienes (eg, eosinophilic airway inflammation[49]), and may offer another pathway to bronchodilation in ED patients with impending respiratory failure. In a Cochrane systematic review of 10 RCTs involving children and adults,[50] although oral leukotriene modifiers did not achieve significant differences in the hospitalization risk in 3 pediatric trials, they significantly improved FEV_1 in 3 adult trials. The combined results of 1 pediatric and 2 adult trials involving intravenous leukotriene modifiers showed a nonsignificant reduction in hospitalization risk (risk ratio, 0.78; 95% CI, 0.61-1.01).[50] Given the mixed quality and heterogeneity of exacerbation severity in these studies, the role of leukotriene modifiers for ED treatment remains unclear.

Parenteral β_2-agonists. The efficacy of adding intravenous β_2-agonists (eg, terbutaline and salbutamol) to inhaled SABA in asthma exacerbation remains uncertain.[7] Within the relevant literature, which is quite heterogeneous and lacks a core set of agreed outcomes,[51] small studies have demonstrated contradictory results.[52-54] A Cochrane systematic review of 3 trials involving children and adults concluded that definitive inference of benefit cannot be drawn in children—and that these agents present no meaningful advantage over inhaled SABA in adults with severe asthma exacerbation.[55] Accordingly, the current EPR3 and GINA guidelines do not recommend its routine use for asthma exacerbations.[7,10] However, the use of intravenous β_2-agonists might have some role in treating children who have poor inspiratory flow and are uncooperative with inhalation therapy after intensive conventional therapy. Australian national guidelines suggest the use of intravenous β_2-agonists as a third-line bronchodilator (if intravenous magnesium is unsuccessful) for life-threatening exacerbations that do not respond to continuous nebulization of SABA.[11] Clinical guidelines also suggest the use of intramuscular or subcutaneous injection of terbutaline or epinephrine in the critically ill or rapidly deteriorating patient[11]; however, these recommendations are not based on robust evidence.

Methylxanthines. Methylxanthines, such as aminophylline, are nonselective phosphodiesterase inhibitors with bronchodilation and anti-inflammation effects. Add-on therapy was once a standard of care for severe asthma exacerbations and is still used in some countries.[56] Yet, the current evidence does not suggest its incremental advantage when added to inhaled or intravenous β_2-agonists. Indeed, in a Cochrane systematic review of 17 RCTs involving adults with asthma exacerbation,[57] adding intravenous aminophylline to inhaled SABA did not yield additional bronchodilation or reduce hospitalization risk but did increase adverse events (eg, arrhythmias and vomiting). In addition, in a meta-analysis of 11 RCTs involving both children and adults,[58] there was no consistent evidence to support the use of either intravenous aminophylline or β-agonists. In this context, the EPR3 and GINA guidelines do not recommend the use of intravenous methylxanthines in the ED,[7,10] whereas the Australian guidelines suggest their use as a third-line bronchodilator for life-threatening exacerbations.[11]

Ketamine. Ketamine—a dissociative agent often used for procedural sedation—has some bronchodilator effects, and is an option for use in critically ill patients with asthma.[59] However, positive findings are mostly confined to case reports and observational studies.[60] A 2012 Cochrane review identified a single trial involving 68 children, and was unable to conclude whether ketamine was an effective treatment.[60] A recently published trial randomized 59 adult patients intubated for severe obstructive lung disease (mostly COPD) to either ketamine or fentanyl infusion and found no difference in ventilatory markers of bronchospasm.[61] Ketamine may be useful to facilitate noninvasive ventilation in a combative patient, and it may also be useful as an induction agent for intubation. However, current evidence does not suggest that it provides clinically meaningful additional bronchodilation.

Empiric antibiotics. Little evidence supports the use of empiric antibiotics for asthma exacerbation in the ED.[62] In a recent study that applied robust causal inference approaches to data of 48,743 children hospitalized for asthma exacerbation, early antibiotic treatment was associated with a longer hospital length of stay, higher costs, and no significant clinical benefit.[63] International guidelines recommend against routine use of antibiotics in the ED except for patients with evidence of bacterial infection, such as pneumonia.[7,10,11]

Limitations in available studies on nonstandard therapies. Although first-line medical treatments for asthma exacerbations are well established, there is a lack of evidence to support the choice of adjunct treatments. Problems with the current literature include small studies, a lack of studies comparing different treatment options, and significant variation in inclusion criteria and outcome measures between clinical trials.[35] Work is underway to develop a core outcome set for future clinical trials in children with severe acute asthma.[35] Given the relatively rare nature of severe asthma exacerbations, it is likely that large multicenter trials will be needed to provide definitive evidence to guide treatment.

Respiratory support for impending respiratory failure

Noninvasive mechanical ventilation. Noninvasive positive pressure ventilation—including biphasic positive airway pressure and continuous positive airway pressure—may be considered for patients who have severe asthma exacerbations but do not require immediate intubation. Although the literature has strong evidence for the beneficial role of noninvasive positive pressure ventilation in patients with acute exacerbation of COPD (eg, reduction of invasive mechanical ventilation and mortality),[64] its role in treating asthma exacerbation remains unclear. In a 2012 Cochrane systematic review of 2 RCTs involving 96 patients with asthma exacerbation,[65] there was no significant difference in the rate of tracheal intubation between the noninvasive positive pressure ventilation and usual medical care groups. Another systematic review of 13 studies including small RCTs also reported insufficient evidence to support (or refute) the use of noninvasive positive pressure ventilation in patients with asthma exacerbation.[64] In contrast, in a recent large observational study of 53,654 intensive care unit patients with asthma exacerbation, Althoff et al[66] applied robust causal inference approaches and found an association between the use of noninvasive positive pressure ventilation and lower risk of receiving invasive mechanical ventilation and in-hospital mortality. Although sufficiently powered, rigorously designed clinical trials are required to determine its role in managing ED patients with asthma exacerbations, a brief trial of noninvasive positive pressure ventilation is reasonable in selected ED patients.[66] Failure of noninvasive positive pressure ventilation may be an indication for intubation and invasive mechanical ventilation.

Invasive mechanical ventilation. Of adult patients hospitalized with asthma exacerbation, 3% to 5% develop respiratory failure requiring mechanical ventilation.[34] The decision to intubate and initiate mechanical ventilation is based on clinical judgment, and is guided by signs of respiratory failure (ie, inadequate oxygenation or ventilation), clinical symptoms (eg, altered mental status and respiratory fatigue), comorbidities, and the clinical trajectory.[7] The primary goals of mechanical ventilation include providing sufficient oxygenation and ventilation while minimizing the risk of dynamic hyperinflation[7] secondary to expiratory airflow limitation and alveolar air trapping.

Dynamic hyperinflation is a common problem that leads to intrinsic positive end-expiratory pressure (PEEP), or auto-PEEP, and hence elevates the airway plateau pressure, leading to barotrauma, increased work of breathing, and risk of cardiovascular collapse due to limitation of venous return. In evaluating dynamic hyperinflation, measurement of plateau pressure is a more accurate measure than that of peak airway pressure. Initial settings of ventilator (eg, tidal volume of 6-8 mL/kg ideal weight, respiratory rate of 10-12 breaths/min, inspiratory flow of 60-75 L/min, PEEP at 5 cm H_2O) may require adjustment to maintain a goal plateau pressure of less than 30 cm H_2O and intrinsic PEEP of less than 10 cm H_2O[67] through, for example, decreasing the tidal volume and respiratory rate, and increasing the inspiratory flow rate, with permissive hypercapnia as the ventilator strategy.

SPECIAL POPULATIONS

Young children

Establishing a diagnosis of asthma exacerbation in young children is often challenging and requires a careful clinical assessment. Objective lung function measurement is unreliable, if not impossible, in this age group.[7] Wheeze is most commonly caused by asthma, but it is not pathognomonic. There is also a considerable overlap between asthma and preschool viral wheezing. The evidence is mixed regarding the role of systemic corticosteroids in treating virus-induced wheezing in preschool children, partially because of the heterogeneity between studies.[68] Altholugh some studies have reported its effectiveness (eg, shorter ED length of stay),[69,70] most have shown no significant effects on the symptom severity or hospitalization rate in young children.[68,71,72] Yet, the question of whether this treatment strategy is beneficial in subgroup(s) of children (eg, atopic children with rhinovirus-induced wheezing[69]) remains unclear. In contrast to the inconclusive evidence on systemic corticosteroids, a 2018 systematic review concluded that in young children (aged 0-4 years) with recurrent wheezing, the use of intermittent ICS with SABA at the onset of acute respiratory infection reduces the risk of exacerbation requiring systemic corticosteroids, when compared with the use of rescue SABA therapy.[73] Accordingly, the 2020 Focused Updates conditionally recommend starting a short course of daily ICS for this patient population.[74]

Infants (aged <12 months) are more likely to have bronchiolitis alone—the most common lower respiratory tract infection among infants.[75] Although these infants may present signs similar to asthma exacerbation (eg, tachypnea and wheezing), it is not feasible to make a diagnosis of asthma. Inhaled bronchodilators are not recommended in classic respiratory syncytial virus bronchiolitis[76]; however, their role in non−respiratory syncytial virus bronchiolitis is unclear.[77] In addition, an ongoing debate exists on how to best classify young children with recurrent wheezing, with efforts to identify a subgroup of children who subsequently develop (or already have) asthma.[78-82]

Generally, the ED evaluation of young children with asthma exacerbation remain the same as described for adult patients (eg, serial examinations and pulse oximetry)[7] except that an objective

TABLE II. Risk factors for fatal asthma exacerbation

Asthma history
Previous severe exacerbations (eg, intubation or ICU admission for asthma)
≥3 ED visits for asthma exacerbation in the past year
≥2 hospitalizations for asthma exacerbation in the past year
ED visit or hospitalization in the past month
Use of ≥3 canisters of SABA per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: Delay in seeking care, sensitivity to *Alternaria*
Social history
Low socioeconomic status or inner-city residence
Illicit drug use
Major psychosocial problems
Comorbidities
Cardiovascular diseases
Other chronic lung diseases
Chronic psychiatric diseases

ICU, Intensive care unit.
Modified from the National Asthma Education and Prevention Program.[7]

lung function measurement using PEF is usually impossible. In addition, although these measurements are useful for some children 5 years or older, a measurement may not be attainable in the setting of exacerbation.[83] Careful attention to clinical signs (respiratory rate, retractions, mental status) is paramount. Given the importance of assessing the disease severity, several risk stratification tools based on the severity of asthma exacerbation have been developed.[84-88] However, a systematic review has indicated that none of the published tools is sufficiently validated for clinical use.[89] ED providers should closely monitor children with frequent examinations and pulse oximetry.

Pregnant women

Asthma complicates 4% to 8% of all pregnancies.[90-92] Furthermore, approximately one-fourth of pregnant women with asthma have an ED visit or hospitalization,[93] with the highest risk during the second and third trimesters.[94] Risk factors for worsening asthma control during pregnancy include greater prepregnancy asthma severity, inappropriate medication use, smoking, obesity, weight increase in the first trimester, and inadequate prenatal care.[92,95] Poor asthma control is associated with increased risks of both maternal and fetal complications (eg, spontaneous abortion, preeclampsia, cesarian section, congenital malformations, preterm birth, and low birth weight).[93,96-101] Children born to mothers with poorly controlled asthma are more likely to develop bronchiolitis during infancy,[102] eczema, and wheezing symptoms,[103] potentially through epigenetic changes.[104] To prevent these complications, rapid treatment of exacerbations is critical.

ED asthma management guidelines do not substantially differ between pregnant and nonpregnant patients.[92,105,106] Yet, a multicenter study of 48 US EDs demonstrated suboptimal acute asthma care in pregnant women (eg, 22% did not receive systemic corticosteroids in the ED and 37% did not receive prescription for systemic corticosteroids at discharge).[107] The potential risk of systemic corticosteroid use during pregnancy (eg, preterm birth, preeclampsia, and gestational diabetes)—which is attributable, at least partially, to confounding by asthma control (ie, uncontrolled asthma leads to both corticosteroid use and apparent adverse outcomes)—is considered smaller than the aforementioned risks of uncontrolled asthma.[92,105,106] Therefore, systemic corticosteroids should be used for pregnant women with asthma exacerbation when indicated.

The elderly

Asthma in the elderly population is an undertreated condition that results in impaired quality of life and lung function. A definitive diagnosis is often delayed because of atypical presentations, overlap with COPD, and presence of coexistent comorbid illnesses,[108] including aspiration, gastroesophageal reflux disease, heart failure, and paroxysmal arrhythmias (Table I). Differentiating asthma exacerbation from an acute exacerbation of COPD is particularly challenging.[109] Spirometry may be helpful in this setting, unless the patient has a severe exacerbation or cognitive impairment. Most elderly patients with asthma reveal incomplete bronchodilator reversibility.[110]

ED DISPOSITION AND POSTDISCHARGE CARE

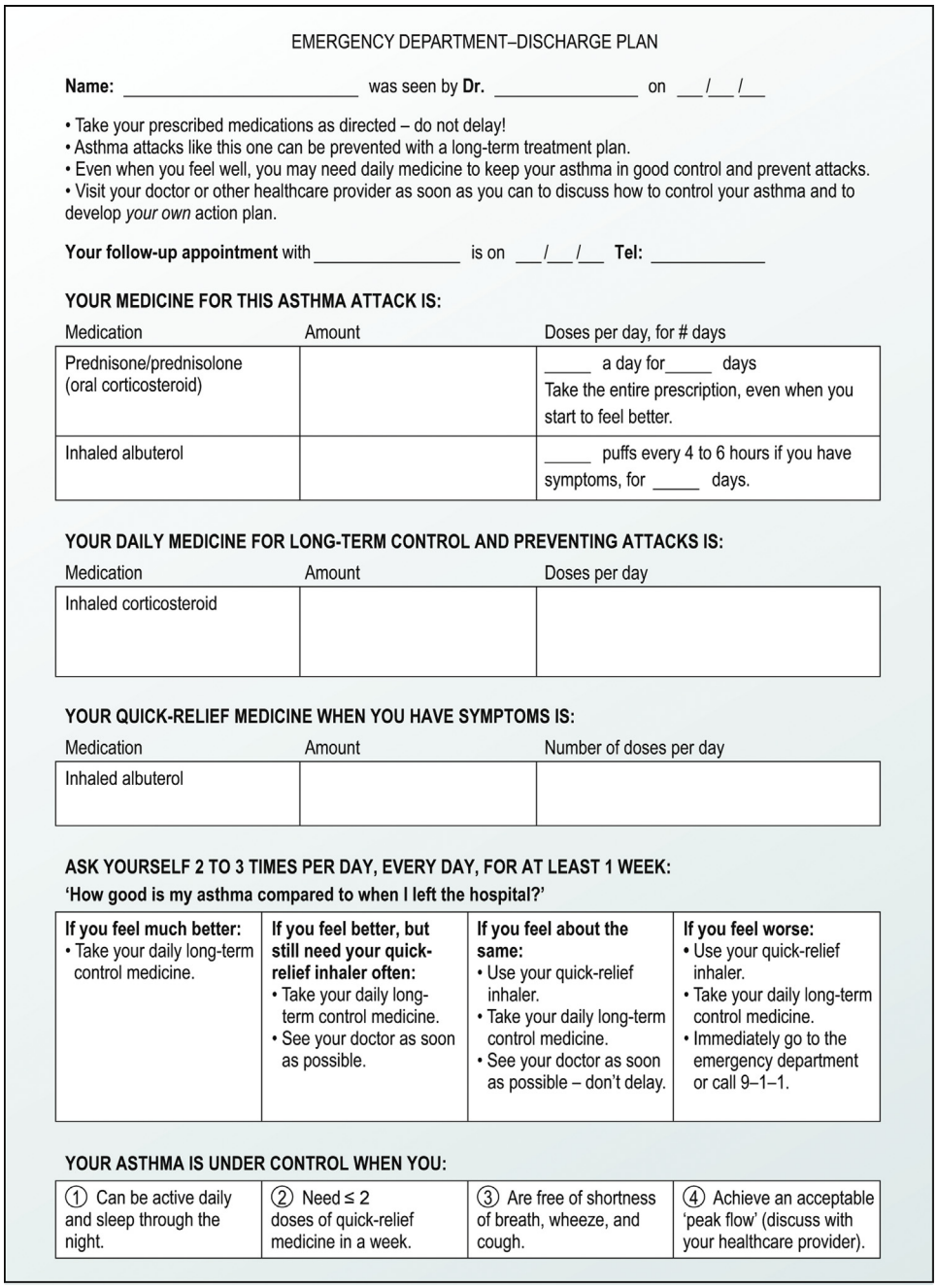
ED Disposition

Identifying a patient who should be discharged or hospitalized is based on clinical judgment, the severity and trajectory of signs and symptoms, response to treatment (including pretreatment and posttreatment lung function measurements), comorbidities, access and adherence to outpatient care, and home environment.[7] Generally, it is appropriate to discharge the patient from the ED when PEF returns to greater than or equal to 70% of predicted or personal best with minimal symptoms.[7] Patients with a lesser degree of response to the ED management (eg, PEF 50%-69% of predicted or personal best) and with mild to moderate symptoms should be repeatedly reassessed while taking the risk factors for fatal asthma exacerbations (Table II) into account. With an improvement in objective measurement, appropriate self-management knowledge/skills, and supportive home environment, such patients can often be discharged home. In addition, extended treatment and serial monitoring in an observation (or short stay) unit may be appropriate. The EPR3 (Figure 1), GINA, and Australian guidelines provide algorithms to guide decision making.[7,10,11]

The immediate objective after ED discharge is prevention of an acute asthma relapse (ie, acute deterioration during an exacerbation). To achieve these goals, ED providers should provide high-quality transitional care, including discharge medications, education, action plans, and referral for an outpatient provider.[7]

Discharge medications

After an asthma exacerbation, residual airway inflammation may last for several weeks, leaving the airways sensitive to inhaled allergens, irritants, and acute respiratory infections. Indeed, 10% to 20% of ED patients with asthma exacerbation have a relapse within 2 weeks after ED discharge.[34,62,111] Accordingly, discharged patients should be treated with systemic corticosteroids (eg, prednisone, prednisolone, or dexamethasone).[7,10,11] In a Cochrane systematic review of 6 RCTs,[112] patients treated with systemic corticosteroids after ED discharge—compared with placebo—had fewer inhaled β_2-agonist use, relapses, and rehospitalizations. Data do not show a clear superiority of intramuscular corticosteroids; however, they may be an option for patients with vomiting or low likelihood of oral corticosteroid adherence.[112]



EMERGENCY DEPARTMENT–DISCHARGE PLAN

Name: _____ was seen by **Dr.** _____ on __/__/__

- Take your prescribed medications as directed – do not delay!
- Asthma attacks like this one can be prevented with a long-term treatment plan.
- Even when you feel well, you may need daily medicine to keep your asthma in good control and prevent attacks.
- Visit your doctor or other healthcare provider as soon as you can to discuss how to control your asthma and to develop *your own* action plan.

Your follow-up appointment with _____ is on __/__/__ **Tel:** _____

YOUR MEDICINE FOR THIS ASTHMA ATTACK IS:

Medication	Amount	Doses per day, for # days
Prednisone/prednisolone (oral corticosteroid)		_____ a day for_____ days Take the entire prescription, even when you start to feel better.
Inhaled albuterol		_____ puffs every 4 to 6 hours if you have symptoms, for _____ days.

YOUR DAILY MEDICINE FOR LONG-TERM CONTROL AND PREVENTING ATTACKS IS:

Medication	Amount	Doses per day
Inhaled corticosteroid		

YOUR QUICK-RELIEF MEDICINE WHEN YOU HAVE SYMPTOMS IS:

Medication	Amount	Number of doses per day
Inhaled albuterol		

ASK YOURSELF 2 TO 3 TIMES PER DAY, EVERY DAY, FOR AT LEAST 1 WEEK:

'How good is my asthma compared to when I left the hospital?'

If you feel much better:	**If you feel better, but still need your quick-relief inhaler often:**	**If you feel about the same:**	**If you feel worse:**
• Take your daily long-term control medicine.	• Take your daily long-term control medicine. • See your doctor as soon as possible.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • See your doctor as soon as possible – don't delay.	• Use your quick-relief inhaler. • Take your daily long-term control medicine. • Immediately go to the emergency department or call 9–1–1.

YOUR ASTHMA IS UNDER CONTROL WHEN YOU:

① Can be active daily and sleep through the night.	② Need ≤ 2 doses of quick-relief medicine in a week.	③ Are free of shortness of breath, wheeze, and cough.	④ Achieve an acceptable 'peak flow' (discuss with your healthcare provider).

FIGURE 2. Asthma action plan. This is a sample asthma action plan that can be used at ED discharge for patients with asthma exacerbation. This document represents expert opinion and its efficacy on asthma outcomes has not been validated. Reproduced and modified from Burks AW, Holgate ST, O'Hehir RE, Bacharier LB, Broide DH, Hershey GK, et al. Middleton's principles and practice. 9th ed. Elsevier Health Sciences; 2019. This figure originates from the National Asthma Education and Prevention Program.[7]

In addition to systemic corticosteroids after ED discharge, ICS is an important drug to prevent future relapses and potential decline in lung function due to future exacerbations.[7,113] In a meta-analysis of 9 RCTs that compared ICSs plus systemic corticosteroids with oral corticosteroids alone after ED discharge,[114] the combined therapy led to a *nonsignificantly* lower risk of relapses (odds ratio, 0.68; 95% CI, 0.46-1.02). Given the strong evidence that long-term ICS therapy lowers the exacerbation frequency in patients with persistent asthma, guidelines recommend initiating ICS therapy in addition to oral corticosteroids at ED discharge for the patient who had not been prescribed ICS before the ED visit.[7,10,11] For patients who were already on ICS, step-up therapy should be considered after evaluating their medication adherence. High-dose ICS *alone* may be considered as an alternative to systemic corticosteroids in patients with mild exacerbation, although a meta-analysis of

RCTs showed no significant difference in the risk of relapse or rehospitalization.[114] However, this does not necessarily imply equivalent efficacy; the current evidence reflects ongoing equipoise.

Asthma education

ED management is an important part of the continuum of asthma care. ED visits for asthma exacerbation offer an opportunity for reinforcement of asthma education.[115,116] Because asthma is characterized by variable expression over time, patients ought to have a plan for asthma control (including self-monitoring), appropriate inhaler use technique (including the use of pMDI with valved holding chamber), and plan in case of worsening symptoms.[117] In a Cochrane review of 12 RCTs of adults with asthma exacerbation, information-only education did not significantly decrease the subsequent risk of ED visits or hospitalizations for asthma exacerbation.[118] In contrast, a meta-analysis of 36 RCTs involving adults demonstrated that self-management education with a review by health care provider decreased postdischarge health care utilization.[119] Likewise, in a meta-analysis of 38 RCTs involving ED children with asthma exacerbation, educational intervention to children and/or their parents significantly decreased the risk of ED revisits and hospitalizations.[120] Collectively, the evidence indicates that integrated education programs (rather than isolated asthma education) may improve postdischarge asthma control and reduce asthma-related health care utilization. In addition, for cigarette smokers (who consist of one-third of ED[121] and hospitalized[122] adult patients with asthma exacerbation) and those who are parent or caretaker of children with asthma, an ED visit provides an opportunity to develop and initiate a plan for smoking cessation.[123]

Asthma action plans

An important part of asthma education involves the development of an asthma action plan. In an RCT of 219 ED children with asthma exacerbation, Ducharme et al[124] reported that, compared with the unformatted prescription, a written action plan coupled with prescriptions increased adherence to inhaled and oral corticosteroids, improved asthma control, and increased physicians' prescription of maintenance ICS and recommendation for medical follow-up. Despite its clinical importance, recent studies also showed the low prevalence of existent written action plan use in ED patients with asthma exacerbation.[8,9,125] These observations collectively suggest that ED providers should develop and review a brief, personalized written asthma action plan with the patient at discharge. International guidelines (eg, EPR3 guidelines[7]; Figure 2) offer helpful examples. Recently, smartphone apps to assist with ongoing asthma management have been developed, although further research is required to determine their effectiveness.[126,127]

Postdischarge follow-up

In addition to asthma education, the ED visit for asthma exacerbation offers an opportunity for facilitating longitudinal care. Indeed, all guidelines underscore the importance of longitudinal asthma care in the outpatient setting.[7,10] For example, the EPR3 guidelines recommend that these patients should be referred for a follow-up care either by a primary care physician or by an asthma specialist within 1 to 4 weeks after the ED discharge.[7] However, studies also suggest that less than half the patients see a primary care physician for follow-up asthma care within 4 weeks after the ED visit.[128-130]

Current evidence on the role of facilitated follow-up is somewhat conflicting. For example, 2 RCTs reported that facilitated referral of ED patients to the primary care providers did not change long-term asthma outcomes.[129,131] In contrast, another RCT in an ED setting by Zeiger et al[132] demonstrated that facilitated referral to an asthma specialist significantly reduced the risk of subsequent ED visits for asthma exacerbation.

Although these studies focused on the efficacy or effectiveness of single or limited elements of asthma care (eg, asthma education, action plans, or facilitated referral), it seems likely that a multifaceted evidence-based care "bundle" would be more effective. Indeed, an RCT of children hospitalized for asthma demonstrated the feasibility of a comprehensive care bundle that is initiated in the hospital.[133] In addition, an RCT of adults with asthma exacerbation reported that, compared with conventional care, multifaceted asthma care intervention for hospitalized patients reduced readmissions as well as health care costs.[134] Although these observations support a cautious optimism that the quality of acute asthma care can be further improved and asthma morbidity mitigated, the role of implementation of evidence-based transitional care in the ED merits further investigation.

SUMMARY

Asthma exacerbations occur in all patients with asthma, across a wide spectrum of chronic asthma severity; they account for a significant portion of ED visits, both in children and in adults. The best strategy for ED management of asthma exacerbation is early recognition and intervention before the exacerbation becomes severe and potentially life- threatening, with the use of both pharmacologic and nonpharmacologic interventions. Evidence-based ED management improves the outcomes in this population with large morbidity and health care burden.[8,9,135] After successfully managing an acutely ill patient, ED management should focus on multifaceted transitional care that optimizes subacute and chronic asthma management. Coordinated care between ED clinicians, primary care physicians, and asthma specialists will help ensure that patients receive the best care possible.

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