

REVIEW ARTICLE

Inpatient Management of Bronchial Asthma for the Hospitalist – A Concise ReviewMichael P. Hunter¹, Suman Vaddi¹, Armin Krvavac¹, Hariharan Regunath^{1,2}, Vamsi P. Guntur³¹ Department of Medicine, Division of Pulmonary, Critical Care, and Environmental Medicine, University of Missouri, Columbia, MO² Department of Medicine, Division of Infectious Diseases, University of Missouri, Columbia, MO³ Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, National Jewish Health, Denver, COCorresponding Author: Michael Hunter, MD. One Hospital Drive, CEC 404, Columbia, MO 65212.
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Abstract: Asthma is a common inflammatory disease of the airways that leads to significant hospital utilization and health care cost around the world. Despite published guidelines, the diagnosis and treatment of acute asthma exacerbation varies widely due to inconsistent compliance with guidelines. We will review the evidence, guideline recommendations, clinical presentation, risk factors, and management of acute asthma exacerbations, including standard and advanced treatment options for refractory cases.

Keywords: Bronchial asthma, inpatient, bronchodilators, steroids, eosinophils

CLINICAL SCENARIO

A 35 year old morbidly obese lady with history of asthma presents to the emergency room with acute onset dyspnea following no improvement with rescue inhalers. On exam she is awake, dyspneic, cyanotic, heart rate 120/min, blood pressure 100/50 mmHg, respiratory rate 30/min, SpO₂ 90% on 10 L/min of nasal oxygen. Chest X-ray had no infiltrates. Accessory muscles of respiration were active and breath sounds were diminished bilaterally. Continuous nebulization with beta-agonist and non-invasive ventilation were instituted. Abnormal laboratory tests showed mild hypokalemia and nasal swab was positive for influenza A. There was no improvement in the

ensuing 30 minutes and she appears exhausted.

INTRODUCTION

Asthma is a chronic inflammatory disease of the airway characterized by airflow obstruction and bronchial hyper-responsiveness. Varying clinical features in a heterogeneous demographic population leads to diverse clinical phenotypes (1). Higher prevalence is seen in women, African Americans, and in those from a lower socioeconomic status (2). In 2016, the Centers for Disease Control and Prevention (CDC) reported that 8.3 percent of the adult population in the United States (> 20 million) suffer from asthma (2). Within the last decade, over 400,000 annual hospital

discharges (14.3 per 10,000 population) and 1.7 million annual emergency department visits were reported among Americans with asthma as the primary diagnosis (2,3). The average cost of a hospital admission for treatment in 2010 was \$9,000 per case, with a total cost of \$2.9 billion (4). The estimated health care (both inpatient and outpatient) cost of asthma in 2011 was \$56 billion (3). Despite specific guidelines for in-hospital management, medical audits have shown inconsistent compliance by healthcare providers (5). We review the evaluation and management of asthma exacerbations in adult patients requiring hospitalizations. Specifically, objective assessment of severe exacerbations, factors that help to determine the appropriate level of care based on severity, management of the asthmatic airway, and discharge planning will be discussed.

CLINICAL PRESENTATION

The diagnosis of asthma is made based on history, clinical features, and objective evidence of reversible airflow obstruction (6). None of the typical symptoms of asthma exacerbation such as breathlessness, cough, wheezing, chest tightness, or worsening exercise tolerance are either sensitive or specific for diagnosis (Table 1) (5). The symptom-free periods are interrupted by episodes of exacerbation precipitated by infection, environmental irritants, cold air, exercise, or other allergens. During severe exacerbations patients often develop chest tightness or heaviness. Table 1 lists the sensitivity and specificity for individual symptoms of asthma. Using a combination of the individual symptoms increases the sensitivity and specificity for diagnosis, but only up to 60% and 66%, respectively (7). Therefore, a comprehensive history is critical for the assessment and diagnosis of asthma. Table 2 lists the signs

and symptoms that suggest alternative diagnoses other than asthma.

Evidence of airflow limitation can be measured by a decline in peak expiratory flow rate (PEFR) or forced expiratory volume in the first second (FEV1), and often increase in symptoms (8,9). Exacerbations, just like symptoms, are caused by a variety of triggers depending on endotype of the asthmatic (i.e. classic eosinophilic or Type 2 vs. non-eosinophilic or Type 1). Triggers and risks for severe exacerbation of asthma are innumerable, of which viral upper respiratory infections have been reported to be the most common (rhinovirus, coronavirus and influenza) (10). Allergen exposures including dust mites, pollen, and animal dander are well known environmental factors that can precipitate asthma (1,5,10,11). Specific populations are at risk for more profound exacerbations and should be within the radar of healthcare providers of first contact. African or Puerto Rican descent, lower socioeconomic status, and pregnancy not only have higher frequency of exacerbations but also do not get hospitalized until symptoms get severe (10,12). Location of residence and air quality have been correlated to a higher incidence of asthma exacerbations and hospitalizations, especially in children (13,14). Therefore, demographic evaluation may be helpful to predict control of asthma and future severe exacerbations requiring hospitalizations. Co-morbid conditions such as obesity, psychologic disease, rhinosinusitis, smoking, food or environmental allergies, LPR, and GERD should also be adequately managed along with the asthma exacerbation (10,12). Many of the alternative diagnoses listed in Table 2 can not only confound asthma diagnosis but also contribute to exacerbations. Therefore, a hospitalized patient found to have an alternative diagnosis should also be evaluated for asthma exacerbation.

Spirometry risk factors for an acute exacerbation include FEV1 <60% predicted and a higher degree of bronchodilator reversibility (12). In those without a prior diagnosis of asthma, presence of risk factors for asthma exacerbation such as objective wheezing on chest exam, personal/family history of atopy, and decreased PEFR during symptomatic episodes can help in making a diagnosis. Increased sputum eosinophils (>3%) or blood eosinophilia (>300/ μ L) likely increase the risk of type 2 asthma exacerbation (15,16). Likewise an elevated fractional excretion of nitric oxide (FeNO) also raise the risk of an acute asthma exacerbation (10).

Once an acute exacerbation has been diagnosed by clinical and/or physiologic deterioration of respiratory function, the next step is to assess the severity. Severity is determined by a combination of symptoms, objective examination and response to treatment (Table 3). It is important to recognize that the rapidity of symptom onset is associated with a higher risk of mortality (17). Multiple studies in the past have compared “rapid onset asthma” (ROA) (symptoms developing <2 hours) to “slow onset asthma” (SOA) with respect to potential triggers, clinical presentation, hospital length of stay (LOS), intensive care unit (ICU) LOS, morbidity, and mortality (17). The ROA group had NSAID (P=0.009) or fume inhalation (P=0.03) as triggers while the SOA group had respiratory infection as the trigger for an exacerbation (P<0.001) (17,18). Some other findings, albeit without statistical significance, included more respiratory arrests at presentations (P=0.062), impaired consciousness (P=0.026), and absent lung sounds (P=0.047) in the ROA group who also received significantly higher doses of steroids in the first 24 hours after admission (263mg vs 194mg prednisone or

equivalent, P= 0.02) (17). The SOA group had significantly longer hospital stays and intubation times (P=0.031 and P=0.005, respectively). This data suggests that the ROA phenotype (more recently being encompassed in the non-eosinophilic or irritant induced phenotype) has a higher association with life threatening presentation (absent breath sounds, altered mentation) but with greater ability for reversal compared with SOA patients (17).

DETERMINING APPROPRIATE LEVEL OF CARE

Risk stratification to determine the level of care is based on history. The most important criteria that increase the risk of life-threatening asthma exacerbation are a prior history of mechanical ventilation (OR 6.69; 95% CI 2.80-15.97) and ICU admission (OR 5.14; 95% CI 1.91-13.86). Additional risk factors for life-threatening asthma exacerbation include increased use of oral steroids leading up to presentation (OR 2.71; 95% CI 1.34- 5.51), history of hospital admission (OR 2.62; 95% CI 1.04-6.58), increased use of nebulizers (OR 2.45; 95% CI 1.52-3.93), and increased frequency of beta-agonist inhalers use (OR 1.67; 0.99-2.84) (11). Of patients who had a fatal asthma attack, 88% had moderate to severe baseline asthma symptoms, 47% had previous hospital admissions for asthma, 44% had psychosocial or learning disability factors, 30% were either current smokers or had current smoke exposure, and only 15% had previous ICU admission (6). Risk stratification of asthmatics becomes more important during an acute exacerbation as it helps determine appropriate level of care needs for the patient. The primary care provider for the outpatient setting and the physician of first contact in the hospital (e.g. emergency medicine providers or hospitalist in case of direct admission) play a vital role

in risk assessment. Patients with mild to moderate exacerbation can be safely managed in the emergency department or as outpatients with bronchodilators and oral steroids. Severe exacerbations should prompt inpatient admission, while life-threatening asthma exacerbations should prompt admission to the ICU. Clinicians have to pay close attention to previously discussed risk factors for life-threatening asthma, and prior history of life-threatening asthma exacerbations. Presence of these risk factors should prompt consideration for increasing level of care regardless of initial presentation (1,5,12).

TREATMENT

Patients with acute asthma exacerbation require prompt treatment and evaluation. The main goals of therapy are to relieve airflow obstruction, improve work of breathing, and maintain oxygenation and tissue perfusion. Key pharmacological components of acute asthma therapy include serial or continuous short-acting bronchodilators and systemic steroids.

Bronchodilators: Beta-adrenergic agonism has long been the mainstay of asthma treatment dating back when ephedra, a Chinese herbal remedy was used for wheezing (19). Epinephrine was the first synthetic bronchodilator in early 1900s; followed by isoprenaline (19,20). Unfortunately, many of the earlier agents exhibited both alpha- and beta-adrenergic agonism, resulting in tachycardia and hypertension (20). The first beta-2 specific therapy, salbutamol, became available in 1969 and remains the most globally used bronchodilator to this day (20). Inhaled short-acting beta-2 agonist (SABA) therapy is the cornerstone of acute asthma management. Inhaled SABA can be administered as frequent as every 15 minutes or as a

continuous nebulization for refractory cases. Adding ipratropium bromide (a muscarinic agonist) to beta-2 agonist therapy provides improved bronchodilation when compared to beta-2 agonist alone (1,5). Lactic acidosis is a known adverse effect of with high doses of inhaled beta-2 agonists (21,22). During asthma exacerbations, both type A lactic acidosis (from anaerobic metabolism due to hypoxia) and type B lactic acidosis (decreased lactic acid metabolism from beta agonists) have been postulated to occur (22). Beta-adrenoreceptor activation causing an increase in plasma glucose and free fatty acids increase pyruvate levels. Free fatty acids also block the conversion of pyruvate to acetyl-coenzyme A. This excess pyruvate is converted to lactic acid by pyruvate dehydrogenase (22). Hence, exercising vigilance for worsening of metabolic acidosis in those receiving frequent or continuous beta-agonists, may be necessary.

Systemic steroids: Corticosteroids are essential in the control of ongoing inflammation and the stabilization of acute asthma exacerbation. The addition of corticosteroids reduces mortality, relapses, and subsequent hospital admission in acute asthma exacerbation (5). A meta-analysis of 12 emergency department studies suggests that early therapy with systemic corticosteroids (within 1 hour) yielded significantly lower rates of hospital admission. Benefit from corticosteroids is manifested >6 hours after administration. Therefore, we recommend continued monitoring in the emergency department for at least 6 hours after corticosteroid administration to determine its assumed favorable impact (5,23). Of note, adults included in this meta-analysis only received IV corticosteroids, so no recommendation can be made on the effect of oral corticosteroids in adults with asthma exacerbation. The most commonly used

dosages of steroids were hydrocortisone 500mg IV (N=1 study) and methylprednisolone 125mg IV (N=5 studies) (23).

For patients admitted to the hospital ward, the recommended doses of corticosteroids are oral prednisolone 1mg/kg (with a maximum dose of 50mg) daily or intravenous hydrocortisone 400mg daily (often dosed as 100mg injections every 6 hours). Currently, there is insufficient evidence to distinguish between intravenous versus oral route of administration. However, the British Thoracic Society recommends oral route of administration as there is no significant difference in efficacy between oral and intravenous corticosteroids (5). Corticosteroid therapy should be continued for at least five days or until recovery (5,24). Both the BTS and the EPR3 guidelines recommend concurrent use of ICS with systemic steroids (1,5). Clinicians should ensure that ICS is at least started prior to discharge and continued thereafter (5,24).

Magnesium Sulfate: Intracellular magnesium, which is important for airway smooth muscle relaxation and possibly mast cell release of histamine, was found to be low in patients with acute asthma exacerbation (25). Serum levels of magnesium have not found to correlate to intracellular magnesium stores, therefore are not markers of risk or intracellular magnesium depletion and should not be monitored (25). A single dose of 1.2-2g of magnesium sulfate IV has been shown to be safe and reduce hospital admission and intubation rates in asthma exacerbation (5). Magnesium sulfate should be considered in patients with PEFr<50% who have not had a significant response to inhaled bronchodilators (5). Repeated doses have not been studied and may result in hypermagnesemia precipitating respiratory muscle weakness. Recent interest in nebulized magnesium in a sub-group of

severe asthmatics unresponsive to standard treatment had prompted meta-analyses suggesting modest benefit (26,27). However, more robust investigations are warranted before we can advise this modality for acute treatment of severe asthma.

Aminophylline/Theophylline: During an acute exacerbation, aminophylline or theophylline does not result in significantly more bronchodilation when compared to inhaled bronchodilators and steroids. The use of these medications is not recommended for acute treatment (1,5). If patients are being treated with these agents on an outpatient basis, it is reasonable to check a serum level to ensure that the patient is within the therapeutic window (1).

Airway management, oxygen and mechanical ventilation: Hypoxemia should be treated with supplemental oxygen in all cases of asthma exacerbation with a goal SpO₂ of 93-95% (1,5,23). If the patient is awake and meets the criteria for a severe asthma exacerbation as defined in Table 3, frequent reassessments are necessary. Ominous signs of “life threatening” asthma in whom intubation should be considered include mental status changes, normalization or high PaCO₂, a silent chest (very severe bronchospasm), escalating oxygen requirements, or failure of response to treatment (12,28). A wide diameter endotracheal tube (size 8 Fr), rapid sequence intubation with ketamine or propofol as the preferred sedating agent, increased expiratory time (by reducing respiratory rate in controlled modes), and increased respiratory flow rate are some considerations while using mechanical ventilation (28-30). Hypercapnia often ensues due to reduction in minute ventilation from reduced respiratory rate and this is allowed (permissive hypercapnia) to avoid worsening of auto-PEEP. In most cases patients tolerate it,

sometimes to pH as low as 7.2 and PCO₂ as high as 90 mmHg. When minute ventilation cannot be decreased on spontaneous modes, increasing sedation and neuromuscular paralysis should be considered to decrease the risk of barotrauma and avoid dys-synchrony (30,31).

Antibiotics: A recent systematic review of antibiotic use in asthma exacerbations evaluated 6 studies and 681 patients and found very limited evidence for benefit from antibiotics during asthma exacerbations in those without signs and symptoms of infection (32). Limitations were an overall low quality of evidence due to a low number of patients overall, poor outcome measures (specifically hospital admission, ICU admission, and repeated exacerbations), and limited information on the side effects of antibiotic use (32). Guidelines recommend against routine use of antibiotics in acute asthma exacerbations (1,5).

Rescue therapies: Medications and interventions such as Heliox (21% O₂ and 79% Helium) may be helpful in the setting of acute exacerbation because helium has a lower density and higher viscosity than nitrogen, both of which allow for more laminar air flow in constricted airways. This offloads the patient's work of breathing, but there is no data supporting routine use of Heliox (5,33). A systematic review concluded that Heliox did not significantly impact the rate of hospital admission (RR 0.83; 95% CI 0.66-1.08) (34). Sevoflurane is an anesthetic agent which causes bronchodilation via a voltage-dependent calcium channel and modulation of intracellular cyclic adenosine monophosphate levels. Multiple case reports have shown promising results of sevoflurane in refractory, mechanically-ventilated asthmatic patients (35). Sevoflurane appears to be well tolerated in children with life-

threatening asthma, with clinical improvement within an hour of administration and improvement in peak pressures, PCO₂, and pH within two hours of administration (36,37).

DISCHARGE PLANNING

Discharge recommendation is primarily based on patient response to the above-described therapies. Improvement in PEFr can be used in conjunction with the clinical assessment to evaluate adequate response. If PEFrs are known for the patient and the PEFr is >70% of predicted value or the patient's personal best, discharge may be appropriate (1,5). Patients who were prescribed systemic corticosteroids should continue them for at least five days (5). Corticosteroid tapers are generally unnecessary if the total duration of therapy is less than seven days, though tapering may be considered in patients with greater severity of asthma (1). If concurrent inhaled corticosteroids are being used, tapering is not necessary if the total duration of systemic steroid therapy is less than ten days (1). Asthma exacerbations frequently represent a failure in chronic asthma care and should therefore be used as opportunities to review the patient's chronic asthma management. Clinicians should review the patient's understanding of the cause of exacerbation and modifiable risk factors for the exacerbation (12). Patient medications should be carefully reviewed before discharge. ICS therapy should be continued in patients who were previously on ICS treatment and should be initiated before discharge in patients who were not previously on ICS treatment (1,5,12,23,24). Additionally, inhaler education before discharge should occur for all patients who have newly prescribed inhalers, change in delivery devices, or exhibit poor inhaler technique (1). The asthma action plan should

be reviewed and revised in every visit (1). All patients should have regular follow up with a health care provider until symptoms and lung function have returned to normal. Recommended follow up interval is within 2-5 days of discharge (1,5). Additionally,

referral to an expert (asthma specialist) should be considered for patients who have been hospitalized for asthma or have recurrent asthma exacerbations within a month of discharge (1,12).

Table 1: Sensitivity and specificity of common symptoms during asthma exacerbations.

Symptom	Sensitivity	Specificity
Cough	16-66%	26-64%
Wheezing	9-76%	34-87%
Dyspnea in adults	11-73%	38-71%

Table 2: Differential diagnoses for asthma exacerbation

Symptoms	Diagnosis
A prominent cough without changes in lung function	Chronic cough syndrome, Paroxysmal vocal cord dysfunction, angiotensin converting enzyme inhibitors or angiotensin receptor blocker intake.
Dizziness/light-headedness/peripheral tingling	Hyperventilation syndrome (dysfunctional breathing disorder)
Prominent nasal symptoms without changes in lung function	Rhinitis
Postural and/or food-related symptoms	Gastro-esophageal reflux disease Laryngo-pharyngeal reflux
Orthopnea*/paroxysmal nocturnal dyspnea*/ edema/known cardiac disease	Decompensated heart failure, obstructive sleep apnea*
Fine crackles on auscultation	Pulmonary fibrosis
Smoking >30 pk/yrs, symptom onset >35 years of age	Chronic obstructive pulmonary disease
Chronic productive cough without wheezing or breathlessness	Bronchiectasis, inhaled foreign body, obliterative bronchiolitis
New onset weight loss or systemic symptoms /hemoptysis	Lung cancer or sarcoidosis

* Nocturnal apneic episodes of obstructive sleep apnea may be mistaken for orthopnea

Table 3: Grading of the severity of asthma exacerbations based on clinical and laboratory criteria.

Clinical features	Mild-Moderate	Severe	Life-threatening
Breathlessness	On walking	At rest	Unable to lie down
Position	Sitting	Sits hunched forward	“Tripoding”
Speech	Phrases	Words	Gasps between words
Respiration	Accessory muscle not used	Hyperinflation, Accessory muscle use	Paradoxical movement
Alertness	Alert	Agitated	Drowsy or confused
Wheeze	Loud; inspiratory and expiratory	Loud; inspiratory and expiratory	Absent, “silent chest”
Heart rate	Tachycardia	HR>120bpm	Bradycardia
Pulsus paradoxus	10-25mmHg	>25mmHg	Absent
PEFR	>50% predicted *	25-50% predicted *<200LPM	<25% predicted *
PaO ₂	>60mmHg	<60mmHg	cyanosis
PaCO ₂	<42mmHg	>42mmHg	NA
SaO ₂ on room air	90-95%	<90%	NA
Acid base status	Respiratory alkalosis	Normal	Respiratory acidosis

* % predicted of best home value if known.

Notes:

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