PRINCIPLES OF MANAGEMENT OF ACUTE SEVERE ASTHMA: A REVIEW OF CURRENT TRENDS

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ABSTRACT

Asthma is a chronic inflammatory disease of the lungs characterized by airway hyper-responsiveness of the bronchial smooth muscle, edema and disruption of the mucosa as well as obstruction of the lumen by mucus leading to repeated episodes of wheezing, shortness of breath, chest tightness, and coughing.

Several treatment modalities exist for the management of asthma, however, in a large proportion of patients it remains uncontrolled. This predisposes these patients to increased risk of severe exacerbations, poor quality of life and high economic burden in the long-run. The primary goals of asthma treatment are to avoid severe asthma exacerbations, to control symptoms and to maintain normal lung function with the lowest effective dose of medication so that unnecessary adverse effects can be avoided.

In spite of the availability of a wide range of controller/reliever therapies, uncontrolled asthma remains a challenge and posits the need for news therapeutic options. This review discusses current global guidelines for the assessment and management of acute severe asthma control and highlights a few novel therapeutic agents which are employed in the management of asthma.

INTRODUCTION

Asthma, is one of the most common chronic respiratory disease affecting close to 10% of adults and about 30% of children in the western world.[1] It has become a global problem affecting about 300 million individuals of all ages and ethnicities with an estimated 250,000 deaths worldwide. Asthma prevalence is increasing especially in young children.[2] It is becoming a major health issue in many developing countries due to the increased incidence of air pollution, fast industrialization, widespread construction work, westernized diet, improved standards of living and more dust mites as well as also becoming one of the leading causes of emergency department visits. Asthma is a chronic inflammatory disease of the lungs characterized by airway hyper-responsiveness of the bronchial smooth muscle, edema and disruption of the mucosa as well as obstruction of the lumen by mucus leading to repeated episodes of wheezing, shortness of breath, chest tightness, and coughing.[3,4] The airflow obstruction caused by asthma is a reversible one that could occur either spontaneously or with the aid of medication.

Acute asthma exacerbations are largely preventable and may indicate poorly managed disease.5It may be defined by its clinical, physiologic and pathologic characteristics, chief among which is wheezing.

Acute severe asthma

Acute severe asthma refers to episodic events of asthma characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing and progressive decrease in lung function. This may be unresponsive to repeated courses of beta-agonist therapy. As such, it is a medical emergency that requires immediate recognition and treatment. Because of a delayed onset time of about 6-12 hours oral or systemic corticosteroids should be administered to patients with acute severe asthma as early as possible to maximize the clinical benefits. Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally as the first presentation of asthma.

ASSESSMENT

Physical examination

Patients with acute severe asthma may present with symptoms such as shortness of breath, inability to speak

in full sentences, tightness of the chest, cyanotic lips and agitation or confusion. Emphasis should be placed on assessing the severity of the patient's asthma as well as the possible complicating conditions that may be accompanying such as pneumonia, pneumothorax, pneumomediastinum, or atelectasis. Severe airflow obstruction can be predicted by accessory muscle use on observation, pulsus paradoxus, refusal to recline below 30°, as well as a pulse >120 beats/min.

Clinical Evaluation

Lung function assessment: Exacerbations of asthmatic episodes are characterized by airflow obstruction on expiration and can be assessed by quantitative evaluation of lung function tests. These measurements include Peak Expiratory Flow rate (PEF) and spirometry and are more reliable indicators of the severity of acute asthma than clinical symptoms alone.[6] PEF assesses the degree of obstruction and can be used to monitor a patient's response to medical intervention over time. PEF values may vary with gender, age, height and ethnicity. [7]) A value less than 200L/min usually indicates severe obstruction.[7]

Oxygenation assesement: Pulse oximetry helps to monitor for hypoxemia in asthmatic patients. Pulse oximetry is recommended for patients with PEF or FEV_1 less than 40% of normal or patients who are unable to perform lung function tests. [6]Arterial blood gases are indicated for patients with PEF less than 25% of the predicted because such patients are at significant risk of hypercapnia or acidosis.[8]

Other assessments: Chest radiographs are generally not obligatory in a setting of acute asthma and in most cases will show pulmonary hyperinflation as should be expected.[9] However, they should only be used to evaluate other suspected causes of the patient's symptoms such as pneumonia, congestive heart failure, pneumothorax. An electrocardiogram is performed for patients with speculated cardiac disorder. Other testing, including exhaled nitric oxide, serum immunoglobulin E (IgE) levels, and sputum testing may be used in the workup of asthma.[10]

Table 1: Classification of Severity of asthma exacerbations

	Symptoms and Signs	Initial PEF (or FEV1)	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF _70% predicted or personal best	Usually cared for at home Prompt relief with inhaled SABA Possible short course or oral systemic corticosteroids
Moderate	Dyspnea interferes with or limits usual activity	PEF 40%–69% predicted or personal best	Usually requires office or ED visit Relief from frequent inhaled SABA Oral systemic corticosteroids; some symptoms last for 1–2d after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF <40% predicted or personal best	Usually requires ED visit and likely hospitalization Partial relief from frequent inhaled SABA Oral systemic corticosteroids; some symptoms last for >3 d after treatment is begun Adjunctive therapies are Helpful

	Symptoms and Signs	Initial PEF (or FEV1)	Clinical Course
Subset: Life threatening	Too dyspneic to speak; perspiring	PEF <25% predicted or personal best	Requires ED/hospitalization; possible ICU Minimal or no relief from frequent inhaled SABA Intravenous corticosteroids Adjunctive therapies are Helpful

Abbreviations: FEV_1, forced expiratory volume in 1 second; ICU, intensive care unit; SABA, short-acting b2-agonist.
Reproduced from National Asthma Education and Prevention Program. Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007 (NIH publication no. 08-4051).

MANAGEMENT OF EXACERBATIONS

The long-term goals in the management of acute severe asthma should be to achieve good symptom control, minimize asthma related mortality, exacerbations, persistent airflow limitation and side effects of treatment.

However, the goals of the patient must also be considered regarding their asthma and its treatment.[13]
Current recommendations are outlined in the 2012 National Asthma and Education and Prevention Program (NAEPP) Expert Panel Report (EPR-3) (coordinated by the National Heart, Lung, and Blood Institute of the National Institutes of Health) and the 2012 Canadian Asthma Consensus Guidelines.[14,15] Goals of therapy include correction of hypoxemia, rapid reversal of airway obstruction, and treatment of inflammation. Begin treatment by giving oxygen to keep the oxygen saturation at more than 90%.

It is important to adequately assess the patency of the patient's airway, breathing and circulation. Any external triggers should be identified and removed. β-agonists which are potent bronchodilators are administered to achieve rapid reversal of airflow obstruction. Anticholinergics may be used to complement this in cases of severe exacerbations or in patients who do not respond quickly to β-agonist therapy. Patient progress in response to treatment should be monitored by serial measurement of lung function. [14]

First-line therapy

Oxygen therapy

One of the goals of management of acute asthma exacerbation is the correction of hypoxemia improving oxygen saturation up to 93-95%. Saturation levels of oxygen in children or adult <90% indicate the need for aggressive therapy. In severe exacerbations of asthma, preliminary data have shown that high concentration oxygen therapy may potentially lead to CO_2 retention.[17] In a randomised controlled trial comparing the effect on the PaCO2 of high concentration oxygen therapy versus titrated oxygen therapy of patients with acute asthma exacerbations, there was significant increase in $PaCO_2$ levels in patients treated with high concentrated oxygen.[19] A titrated oxygen regime is recommended in the treatment of severe asthma, in which oxygen is administered only to patients with hypoxaemia, in a dose that relieves hypoxaemia without causing hyperoxaemia.[19]

β2-agonists

β2-agonists are potent bronchodilators. They act on β receptors to relax bronchial smooth muscle. Short-acting β agonists (SABA) are recommended first line therapy for management of acute asthma exacerbations.[14] Inhaled SABA therapy should be administered frequently for patients presenting with acute asthma.[13] Short-acting β2-agonists and inhaled short-acting anticholinergics (SAAC) have become effective therapies for adult patients with acute asthma exacerbation who present to the emergency department. A systematic review and meta-analysis comparing the outcome of combined inhaled therapy (SAAC + SABA) versus SABA alone showed reduced hospitalization and improve pulmonary function in adult patients with severe asthma exacerbations with increased risk of hospitalization compared to those with mild-moderate exacerbations with lower risk for hospitalization.[20] β2-agonists should only be used for the relief of acute symptoms. If used on a chronically, they can cause desensitization and tolerance. Some adverse effects associated with β2-agonists include tremor, tachycardia, palpitations, hyperglycemia, and hypokalemia. [21]Current evidence does not support the use of intravenous β2-agonists for the treatment of acute severe asthma.[22]

Short-term side effects of β-agonists include tachycardia and hypokalemia. Long-term adverse effects include sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death.[23] In a study comparing the long-term use, of b-adrenergic agonists with placebo, b-adrenergic-agonists significantly increased the risk for cardiovascular events (relative risk, 2.54; 95% confidence interval, 1.59–4.05).[24]

Patients with mild asthma who have been prescribed as-needed low dose ICS-formoterol combination may require increased doses of the ICS-formoterol in the event of a worsening event of asthma. This reduces the risk of severe exacerbations requiring OCS by two-thirds when compared with SABA-only treatment.[25] Patients who have been prescribed inhaled short-acting β2-agonist (SABA) as their reliever may require repeated doses of SABA for temporary relief until the cause of worsening symptoms passes or the controller medication can now take effect.[13]
However, the use of SABA as reliever therapy is less effective in preventing a progression of worsening asthma event to severe exacerbation requiring OCS than the use of low dose ICS-formoterol reliever with or without a daily maintenance controller.[26] A repeated use of SABA for over 1-2 days may be an indication for poor control of asthma and may warrant a need to review and possibly increase the controller treatment especially if there has been a lack of response to SABA therapy.[13]

Systemic Corticosteroids

Onset of corticosteroids action may take up to 6 hours to become clinically evident.[27] In acute care settings, corticosteroid therapy should be utilized in all but mildest exacerbations in adults, adolescents and children (6-11 years).[28-30] Early systemic corticosteroid intervention is advised within 1 hour of presentation to the emergency department of the hospital.[29] This therapy is important for patients with a history of poorly controlled asthma as well as those already receiving oral corticosteroids.

It is also recommended for moderate or severe asthma, or if β2-agonist do not fully correct decline in pulmonary function.[13] A short course of corticosteroids for asthma exacerbations significantly decreases the rates of relapses and use of short acting β2-agonists.[29] Current guidelines recommends daily doses of OCS equivalent to 50 mg prednisolone as a single morning dose, or 200 mg hydrocortisone in divided doses, for adults. For children, an OCS dose of 1-2 mg/kg up to a maximum of 40 mg/day is suggested.[30] Systemic corticosteroids may be considered in patients with good response to short acting β2-agonists.[14] Following discharge from the ED, patients should be given a course of corticosteroids for 3 to 10 days to prevent relapse.[29] Systemic corticosteroids come in varying forms, including oral, intravenous, and intramuscular. However, the efficiency of oral corticosteroids is equivalent to the intravenous form.[31-33]. OCS are preferred because they are less invasive.[29] Intravenous corticosteroids are recommended for critically ill patients as well as patients who may be intolerant of the oral form.

In such cases, hospitalized patients are given 40 to 60 mg of methylprednisolone intravenously every 12 to 24 hours with higher doses of 60 to 80 mg of methylprednisolone every 12 to 24 hours for critically ill patients.[41] Long-term use of systemic corticosteroids must be discouraged. Indication only exists for the most severe cases of asthma. The side effects of chronic corticosteroid use are significant and include immune suppression, adrenal suppression, growth suppression, Cushing syndrome, and cataracts.[14]

Magnesium Sulfate

Evidence shows the inhibitory effect of magnesium on calcium influx into smooth muscle causing bronchodilation.[34] Magnesium also acts on neutrophils to decrease inflammation.[34] A 2009 Cochrane review found that intravenous magnesium sulfate significantly improved pulmonary function and decreased hospital admission rates in patients suffering from severe asthma.[35] A single 2 infusion over 20 minutes reduced hospital admission in some patients, including adults with FEV_1 <25-30% predicted at presentation; adults and children who fail to respond to initial treatment and have persistent hypoxemia; and children whose FEV_1 fails to reach 60% predicted after 1 hour of care.[35-37] Current guidelines however do not recommend its routine use in asthma exacerbations. In a meta-analysis of randomized controlled trials (which excluded patients with severe asthma), addition of intravenous or nebulized magnesium showed no benefit compared with placebo in the routine care of asthma exacerbations in adults and adolescents.[38-39]

Methylxanthines: Aminophylline and Theophylline

Theophylline, a methylxanthine acts by relaxing bronchial smooth muscle, anti-inflammatory effects, stimulation of the medullary respiratory center. Other effects include: increasing heart muscle contractility and efficiency, increasing heart rate, increasing blood pressure and increasing renal blood flow.[1] In view of the poor efficacy and safety profile, and the greater effectiveness and relative safety of short-acting β2 agonist, intravenous aminophylline and theophylline should not be used in the management of asthma exacerbations. In patients with severe asthma exacerbations, aminophylline treatment does not improve outcome compared to short-acting β2

agonists alone

Helium Oxygen Therapy

Helium oxygen therapy known as Heliox is a blend of 70-80% Helium and 20-30% oxygen having a lower gas density than air. Heliox acts by potentially decreasing the resistance to airflow and enhancing the delivery of nebulized bronchodilators to aid their effectiveness.[40,41]

Current guidelines do not recommend helix for initial or routine management of asthma. However, heliox driven albuterol nebulizations should be given in cases of life threatening exacerbations or if exacerbations remain severe up to 1 hour after conventional therapy.[6, 13] Some studies have shown improvements in patients with patients with severe exacerbations treated with heliox-driven albuterol nebulization. In a randomized controlled trial involving 59 adults with severe asthma, it was found that there were significant improvements in FEV1 in those patients treated with nebulized bronchodilators with heliox with largest gains in those whose received it sitting upright and leaned trunk forward at an angle of 50° to 60°.[41]

Self-Management of Asthma exacerbation

Asthmatic patients at risk for exacerbation should be provided with guided self-management education. This should include monitoring of symptoms and/or lung function, a written asthma plan and regular review by the patient's physician.[15] A written asthma action plan is vital to patient recognition and appropriate response to worsening asthma. It should include specific instructions to the patient about changes to reliever and controller medications as well as the use of oral corticosteroids and when and how to access medical care in the event of an exacerbation. A meta-analysis of randomised controlled trials (n=26) evaluating asthma action plan as part of asthma self-management education was carried out. It revealed that individualised written action plans based on personal best PEF, using 2-4 action points and recommending both ICS and OCS for treatment of exacerbation consistently improved asthma health outcomes.[16] Changes in attitude, behaviour and lifestyle may play a significant role in the management of asthma.[9],[10]

It is imperative for clinicians to educate their patient on early recognition and treatment of asthma exacerbation. Immediate treatment should begin with inhaled bronchodilators if symptoms begins to appear and their PEF decreases to less than 80%. PEF should be reassessed after initial bronchodilator treatment. PEF or FEV_1 is used to classify the severity of asthma in patients.

Non-Pharmacological Management

Non-invasive positive pressure ventilation (NPPV)

In the management of acute diseases, non-invasive positive pressure ventilation is best delivered with a tight-fitting full face mask amidst other forms of delivery. While the NPPV, a promising modality works well for acute exacerbations of COPD and cardiopulmonary edema, its routine use for acute asthma cannot be recommended.[42]

However, it may be considered for a stable asthmatic who is tiring from high respiratory demand and is expected to recover within the next few hours.[43] The goal is to support and reduce the patient's respiratory effort in order to buy time for other treatments to take effect and possibly avoid intubation.[44]

Invasive ventilation

A subset of severe asthmatics requires invasive ventilation in a critical care setting. The decision to intubate a patient with a condition of life-threatening asthma is based on clinical judgment. No single data point should be used to substitute for clinical judgement. The indications for intubation include worsening hypercapnia, exhaustion, and changes in mental status; absolute indications being respiratory arrest and coma.[1] Warning signs that a patient will need intubation include decreasing level of consciousness, cyanosis, deterioration of FEV_1 or PEF, inability to maintain oxygenation by mask, respiratory muscle fatigue, and cardiac instability.[43]

Intubation should be done by an experienced clinician, ideally with a large-bore endotracheal tube (≥8.0 mm).[7] Rapid sequence intubation (RSI) is the preferred approach, because the patient is typically exhausted with little physiologic reserve. The clinician should anticipate rapid oxygen desaturation with RSI, and use pre-oxygenation or positive pressure ventilation to optimize respiratory status. Ketamine is the induction agent of choice for sedation and intubation of an asthmatic patient, because of its bronchodilating properties.[45,46] Intravenous ketamine is given at a dose of 1 to 2 mg/kg at a rate of 0.5 mg/kg/min and results in general anesthesia without respiratory depression.[47]

Management of Life threatening (Severe acute asthma)

Status asthmaticus is an acute, severe exacerbation of asthma that is persistent, intractable and remains unresponsive to conventional therapy initially with bronchodilators and systemic corticosteroids. This condition can progress to hypoxemia, hypercarbia and respiratory failure.[48] Such patients must be started on early intensive therapy including β2-agonists, anticholinergics, and systemic corticosteroids. In a systematic review comparing relapse rates and adverse effects of oral prednisone vs. oral dexamethasone for acute asthma exacerbation in pe-

diatric patients, it was found out that while both prednisone and dexamethasone have similar relapse rates when used, dexamethasone was associated with lower incidence of vomiting as compared to prednisone.[49]

Heliox-driven nebulization of bronchodilators and intravenous magnesium sulfate are recommended adjunctive treatments for life-threatening asthma exacerbations or for severe exacerbations that fail to respond to conventional therapy within the first hour.[11] Continuously nebulized albuterol delivered by heliox was associated with a greater degree of clinical improvement compared with that delivered by oxygen among children with moderate to severe asthma exacerbations.[50] Ketamine is a dissociative agent that dilates bronchial smooth muscle and increases circulating catecholamines. Ketamine reduces bronchospasm and can help delay the need for intubation.[51,52] Several case reports of patients with status asthmaticus treated with intravenous ketamine have shown promising results. In these studies, ketamine was given as an intravenous bolus of 0.5 to 1 mg/kg, then as an infusion of 0.5 to 2 mg/kg over 1 hour. These patients failed to improve with conventional therapies, but responded successfully to ketamine.[53,54] Ketamine has a good safety profile and a very low risk of major adverse events;[12] however, there is a paucity of high-quality evidence, which prevents its routine use in asthma [55]. If the patient continues to deteriorate despite maximal medical therapy, noninvasive ventilation or endotracheal intubation with mechanical ventilation should be considered.

CONCLUSION

In the light of our understanding of the pathophysiology asthma, the use of inhaled corticosteroids remains the cornerstone of treatment in the therapeutic management of chronic asthma. Steroids help to improve airway inflammation, lung function and control asthma symptoms in most patients. However, some subset of patients will require additional therapy. Patient education in self-management of asthma is advocated for optimal treatment. Careful assessment of the underlying pathophysiology and individualized treatment goals are vital to patient response to treatment.

Novel therapeutic agents which can act on specific components of the inflammatory pathway in asthma management are developing. In addition, newer agents in combination with already established therapies. The future management of asthma may well involve the use of these newer agents in combination with more established. Current management approaches require patients and families to effectively carry on with complex pharmacologic regimens, institute environmental control strategies, detect and self-treat most asthma exacerbations, and communicate appropriately with health care providers therapies, after their further development and establishment of efficacy

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