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Review

Exacerbations of severe asthma: a focus on steroid therapy

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Summary. Bronchial asthma remains one of the most common chronic diseases in the world; approximately 10% of patients shows exacerbations severe enough to be judged life-threatening, whereas around 2-20% of patients are admitted to the Intensive Care Unit (ICU). Acute severe asthma is a dangerous condition where the deterioration of the asthmatic exacerbation usually progresses over days or weeks, although in a few patients over hours or even minutes. Morbidity and mortality are mainly related to the underestimation of the severity of the exacerbation, delay in referring to hospital and inadequate emergency treatment. The cornerstone measures of therapy for acute severe asthma are oxygen supplementation, as to achieve arterial saturation >90%, and repetitive or continuous administration of bronchodilators (short-acting inhaled β2-agonists and ipratropium bromide) and corticosteroids. Despite extensive clinical experience in treatment of chronic asthma with steroids, there is considerable uncertainty about the accurate use of these agents for treatment of acute severe asthma in emergency settings.

Key words: exacerbations of severe asthma, corticosteroid therapy, tapering

Introduction

Asthma is one of the most common chronic diseases in developed countries (worldwide prevalence 7-10%) and it is also a frequent reason for urgent care and Emergency Department (ED) visits (1-10). Approximately 15-25% of ED patients with asthma will require admission to the hospital, and, among those discharged from the ED after apparently successful treatment, about 10-20% will relapse within the subsequent 2 weeks (8,9,11).

Asthma is a chronic inflammatory disease characterised by reversible airflow obstruction in response to a variety of stimuli. The hallmark of an asthma attack is the progressive airway shrinking due to airway edema, inflammation, luminal secretions and increased bronchiolar smooth-muscle tone (1-6,9,12).

All patients with asthma are at risk for exacerbations characterized by a progressive increase in breathlessness, cough, wheezing, or chest tightness, and by a decrease in expiratory airflow, that should be documented and quantified by PEF (peak expiratory flow) or FEV_1 (forced expired volume in one second) measurement, particularly at night or in the early morning (1-3,9,10).

The most common reasons for Emergency Department asthma presentations include a superimposed upper respiratory tract infection, environmental allergens or poor control of chronic asthma (6).

Severe asthma definition

Severe asthma is a term that encompasses all forms of asthma that do not respond to standard therapy with high doses of inhaled corticosteroids in combination with other medications including long-acting beta-2-agonists and leukotriene-receptor antagonists (13). It is considered a heterogeneous disease in which a variety of clinical, physiological and inflammatory markers determine disease severity (14). Pivotal studies in the last 5 years have led to substantial progress in various areas, including a more accurate definition of truly severe refractory asthma (15,16), and classification of the disease into distinct clinical phenotypes.

The World Health Organization consultation on severe asthma has developed a uniform definition for severe asthma (16), and defines it as: *'Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)*". This global definition includes three subgroups of severe asthma: untreated severe asthma, difficult-to-treat asthma and treatment resistant severe asthma.

Asthma exacerbations definition

Exacerbation is currently the preferred term to describe the acute episodic deterioration of asthma for clinical and scientific use. Patients usually prefer the term 'attack'.

An American Thoracic Society/European Respiratory Society (ERS) Task force recently reviewed the extensive literature on the definition of asthma exacerbations (17) and recommended that severe asthma exacerbations be defined as 'events that require urgent action on the part of patients and physicians to prevent a serious outcome, such as hospitalization or death from asthma'. Exacerbations were further graded into severe and moderate, whereas mild exacerbations were not considered a useful term.

The Task Force recommended definition of a severe asthma exacerbation is at least one of the following: use of systemic corticosteroids or increase from a stable maintenance dose for at least 3 days, or hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.

The Task force defined moderate asthma exacerbations as 'events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe'.

Patterns of exacerbations

Asthma exacerbations follow a definable pattern (18) where there is an abrupt and progressive decline in lung function (phase 1), that can vary in both acuity of onset, rate of decline, and extent of decline. This occurs on a background of maintenance asthma (phase 0), that can also vary in stability, extent of variation, and overall level of lung function. The exacerbation can then progress to death, or to recovery (phase 2). Recovery can be rapid, or in some cases, protracted, with a delayed return to baseline (phase 3). These phases are important as they imply different mechanisms, and potentially different types of intervention. Most severe asthma exacerbations leading to hospitalization are associated with viral respiratory infection, most often by rhinovirus (19). There is also evidence of synergy between viral infection and other triggers such as allergen exposure that may be important in atopic adults (20).

Future risks of exacerbations

Severe asthma exacerbations have longer term consequences. These include a higher risk for further exacerbations and an accelerated decline in lung function. In a prospective observational study, Bai et al. found that one exacerbation per year leads to further 30 mL decline in FEV_1 (21). Interestingly, both future exacerbation risk and loss of lung function may be modified by optimal asthma therapy with inhaled corticosteroid. A *posthoc* analysis of the START ("inhaled Steroid Treatment As Regular Therapy in early asthma") study, found that the accelerated decline in lung function in adults who had a severe exacerbation was reduced in those treated with budesonide (22).

Over the last decade, the aims of asthma management have changed to focus on achieving and maintaining good asthma control and reducing future risks, such as decrease in lung function, asthma exac-

erbations, hospitalizations, death, and adverse effects from treatment. The benefits of good asthma control include a variety of asthma outcomes that are important to both patients and society. These include no restriction in lifestyle, better physical fitness and quality of life, reductions in patients' perception of the asthma burden, health care resource use, and lower risk of exacerbations, hospitalizations, and death.

The general agreement is that bronchodilators and systemic corticosteroids are first-line agents for acute asthma (7), but there are some uncertainties about the route of administration, optimal dose and duration of treatment with steroids (23).

Pathophysiology

Asthma is a complex, chronic inflammatory lung disease that is characterized by bronchial hyperresponsiveness to the inhalation of non-specific irritants and paroxysmal airway obstruction by dense secretions, thickened smooth muscles, edema, and bronchial wall inflammatory infiltration (particularly lymphocytes and eosinophils) (9,24).

Common risk factors include exposure to allergens (domestic dust mites, animals with fur, cockroach, pollens, molds); smoke, occupational irritants; air pollution; respiratory infections; exercise, strong emotional distress; chemical irritants and drugs (such as aspirin and beta blockers).

Hypoxemia is common in every moderate and severe asthmatic crisis because widespread occlusion of lower airways leads to the development of extensive areas of alveolar units in which ventilation is severely reduced but perfusion is maintained (9).

In the early stages of acute severe asthma, analysis of arterial blood gases usually reveals hypoxiemia, hypocapnia and respiratory alkalosis. As the severity of airflow obstruction increases (FEV_1 values lower than 25% of predicted normal) $PaCO_2$ first normalizes and subsequently increases, with consequent acidosis, because of patient's respiratory exhaustion (9).

Even cardiovascular status and function are deeply altered in acute severe asthma: in expiration, because of the effects of dynamic hyperinflation, the systemic venous return significantly decreases, and the large negative intrathoracic pressure generated during inspiration increases left ventricular afterload by impairing systolic emptying (11).

Clinical and functional assessment of severe asthma exacerbations

Patients presenting to the Emergency Department with asthma should be evaluated and quickly triaged to assess the severity of the exacerbation and the need for urgent action (1-3,5,9).

The characteristics of severe asthma attacks that can be seen in the ED are listed in Table 1.

Therapy

Acute asthma is a medical emergency that should be promptly treated. The severity of asthma exacerbations determines the treatment administered (1-3,5,6).

The goals of treatment are to maintain adequate arterial oxygen saturation with supplemental oxygen, to relieve airflow obstruction with repetitive administration of rapid acting inhaled bronchodilators (b_2-agonists and anticholinergics), to reduce airway inflammation and to prevent future relapses with early administration of systemic corticosteroids (12,25,26).

Oxygen treatment is recommended for most patients who present with severe exacerbation in order to

Table 1. Common features of severe asthma exacerbations as can be seen in a ED setting.

Variable	Severe exacerbation	Immininent respiratory arrest
Symptoms and signs:		
Dyspnea	At rest	
Speech	Single words	No words
Alertness	Agitated	Confusion
Wheeze	Present/loud	Silent chest
Respiratory rate	>30breaths/min	
Heart rate	>120 beats/min	Bradycardia
Use of accessory muscles	Evident	Abdominal paradox
Parameters:		
Sao2	<90%	
Paco2	>42 mmHg	
Pao2	<60 mmhg	

maintain oxygen saturation greater than 90% (>95% in pregnant women and in patients with coexistent cardiac disease) (1-6,9,27,28).

The overall goal of emergency department care is to provide safe and effective treatment for the bronchospasm associated with the acute presentation and then to initiate effective anti-inflammatory treatment (1-6,8,9,11,23,27-30).

It is generally accepted that bronchodilators (b_2-agonists: salbutamol) and anti-inflammatory medications (systemic corticosteroids) are first-line agents for acute asthma.

Short-acting b_2-adrenergic agonists should be immediately administered on presentation (usually through a nebulizer), because of their strong and rapid effect on relieving bronchospasm and associated breathing dysfunction (1-6,8,9,11,27-29,31).

In addition to treatments that improve immediate bronchoconstriction, early use of anti-inflammatory drugs is the cornerstone of appropriate treatment to stop airway inflammation and hasten resolution of the asthma exacerbation (1-6,8,9,12,26,27,29,30,32).

However, there are numerous controversies about the use, dose, frequency and route of delivery for corticosteroids in acute setting.

Furthermore, despite publication and revision of international guidelines for the diagnosis and management of asthma, significant gaps persist between evidence-based emergency asthma management guidelines and clinical practice (29).

Corticosteroids in early treatment of acute severe asthma: to use or not to use?

Corticosteroids have been used in the treatment of asthma since 1950 (33). Because airway inflammation, and consequent edema and secretions, appear to be central in the pathogenesis of asthma, it is reasonable to use agents that suppress this process, such as corticosteroids (1-8,10,11,29,33).

The favourable effects observed with these drugs in the chronic and subacute phases of asthma are unquestionable, but there is still an unresolved debate about the use of corticosteroids in early treatment of acute asthma for ED patients (1-8,10,11,29,33).

The most important Guidelines for the emergency management of asthma, Global Initiative for Asthma (GINA 2006), National Heart, Lung and Blood Institute (Bethesda 1997 revised 2007), British Thoracic Society (BTS 2008), Canadian Association of Emergency Physicians and the Canadian Thoracic Society (CAEP/CTS Beveridge 1996) and numerous placebo-controlled randomized trials (Fanta 1983, Littenberg 1986, Stein 1990, Rowe 1992, Lin 1999) recommend the use of systemic corticosteroids to speed resolution and reduce relapse for most patients with exacerbations that necessitate treatment in the ED, especially who have severe asthma and who do not show a rapid response to initial therapy with an inhaled beta$_2$-adrenergic agonist (1-9,12,25,26,29,31,32,34-40).

Rowe et al in a recent meta-analysis have investigated the effect on admission rate and pulmonary function of any form of systemic corticosteroids (intravenous, oral and intramuscular) early administered in the course of treatment in patients presenting to the ED with acute asthma; randomised controlled trials were identified from the Cochrane Airways Group Asthma Register and twelve studies involving 863 patients, 435 on corticosteroids and 428 on placebo, were included (30). The results of these reviews indicate that the early use of systemic corticosteroids within 90 minutes of presentation to an ED significantly reduces admission rates compared with placebo. This benefit was more pronounced for those patients who were not recently treated with oral corticosteroids, those experiencing a severe exacerbation, and in whom inhaled short-acting b_2 agonist do not fully correct the decrement in peak flow (6,7,23,27,32,39,40).

Since the corticosteroids produce their effects on cells by an action on glucocorticoid receptors, that alter transcription through direct DNA binding, their benefits are not usually observed before some hours, so early administration is necessary (within 90 minutes of arrival) (1-7,9,10,26,29,34,37).

Other *non-genomic* aspects of steroid pharmacology might be important in the early phase of treatment, including effects on the microvasculature with inhibition of edema formation in the airways and reversal of b_2-receptor subsensitivity (41).

All these studies show that the early use, as compared with non-use, of systemic corticosteroids is associated with a more rapid improvement in lung func-

tion, fewer hospitalization, and a lower rate of relapse after discharge from the ED (level B of evidence), with few adverse effects both in adults and in children (1-8,27,29,30,40,42-46).

Furthermore, there is evidence that the regular use of long-acting b_2-agonist, salmeterol and formeterol, cornerstones of chronic asthma therapy, is associated with development of subsensitivity to their bronchoprotective and bronchodilator effects; this airway subsensitivity has been shown to be associated with downregulation of lymphocyte beta$_2$-adrenoceptors, and this condition may be rapidly reversed by using systemic corticosteroids. A recent study demonstrated that the same acute facilitatory effects occur when using a bolus dose of inhaled corticosteroid (47). Thus, in acute asthma, systemic corticosteroids should be administered as soon as possible, in order to restore normal airway sensitivity, particularly in patients who present severe asthma and do not respond to b_2-agonist (8,9,26,32,47-49).

Oral or intravenous corticosteroids therapy?

There has been some debate over the use of intravenous versus oral corticosteroids in the ED. However, there is no conclusive evidence from controlled trials or meta-analyses aimed at identifying clinically meaningful or statistically significant differences in FEV_1, length of hospital stay or side effects between patients treated with oral or intravenous corticosteroids regimens (1-6,8,23,26,27,32,42,50).

Oral prednisone and methylprednisolone are rapidly absorbed with virtually complete bioavailability, and their efficacy, when comparable doses are administered, is similar to intravenous methylprednisolone (27).

Therefore the debate should be focused on identifying which patients require the intravenous route compared with the oral route: in the absence of conditions expected to interfere with gastrointestinal absorption (i.e vomiting, diarrhoea) and in patients with normal mental status oral administration is preferred. Oral route is the first choice also for children because it is painless and better tolerated; the major disadvantage of this route is its bitter taste that could impair compliance (1-6,27,43).

Until further evidence is available, it seems reasonable to select oral agents as the first-line choice while reserving intravenous corticosteroids for individuals who are unable to swallow, are obtunded or intubated or are unable to tolerate oral medications (1-4,6,27).

A randomized, double-blind, controlled clinical trial in 1998 showed that a single dose of triamcinolone diacetate, 40 mg intramuscular, produced a relapse rate similar to that of oral prednisone, 40 mg/day over 5 days, after ED treatment of exacerbations of asthma (51,52).

In conclusion the evidence supports that oral corticosteroids are as effective as those parenterally administered (1-6,8,12,26,27,29,32,50,53).

High dose versus low dose of corticosteroids

Many studies have analyzed the optimal dose of corticosteroids in the treatment of acute severe asthma (1-6,8,25,26,54,55).

Emerman et al. analyzed 150 patients presenting to the ED with acute asthma, that were randomized to receive either 100 or 500 mg of methylprednisolone intravenously; they concluded that the higher dose does not appear to lead to a decrease in hospitalization or to a greater improvement in pulmonary function (41,54,55).

Although the optimal dose of corticosteroid is not know, pooled data from controlled trials involving patients observed in the ED have shown no significant advantage of doses greater than 100 mg per day of prednisone equivalent (1-5,25-27,40,50,54,56).

A recent Cochrane Collaboration review by Manser et al, in which 344 patients have been studied, has shown that daily doses of 80 mg of methylprednisolone or 400 mg of hydrocortisone appear to be sufficient in the initial management of acute severe asthma and that higher doses do not appear to offer an obvious therapeutic advantage (25,40,41).

Methylprednisolone is the more expensive of the two drugs but it has less mineralcorticoid activity (4,57).

Although high doses of corticosteroid are usually safer, the more is not necessarily the better in acute severe asthma. The major side-effects of corticosteroids are transient hyperglicemia, acute psychosis, hyperten-

sion, hypokalemia, susceptibility to infections, peptic ulcer disease and acute myopathy especially in intubated and mechanically ventilated patient; sudden deaths have also been reported with high-dose pulse therapy, presumably related to cardiac arrhythmias triggered by acute electrolyte shifts (9,41,44-46,56).

The British guidelines advise the use of 40-80 mg of prednisolone or 400 mg daily parenteral hydrocortisone (100 mg every 6 hours) for the treatment of acute asthma in adult, while recommend to use a dose of 30-40 mg of prednisolone for children aged >5 years, a dose of 20 mg for children aged 2-5 years and 10 mg of soluble prednisolone for children aged less than 2 years; intravenous hydrocortisone (4 mg/Kg repeated every four hours) should be reserved to severely affected children who are unable to retain oral medication (2).

Substantially all these studies clearly confirm that high doses of corticosteroids offer no further benefit over low dose in patients with acute severe asthma (25,40,56).

What is the duration of corticosteroid therapy in post-ED care?

The use of short courses of oral steroids after discharge from the emergency room has been previously recommended (42).

For patients with acute severe asthma, the optimal duration of systemic steroid therapy, essential to effect complete resolution of symptoms and return of lung function to baseline, varies from different patient and attack, and it is an important clinical question (27,58).

Guidelines strongly encourage treatment with systemic corticosteroids after discharge from the ED for an asthma exacerbation to reduce the high risk of relapse (about 12-17% of patients relapse within 2 weeks from discharge) (1-6,8,29,39,56,58,59).

In a Cochrane systematic review, that compared post-ED corticosteroid treatment to placebo, it emerged that fewer patients in the corticosteroid group relapsed within the first week and also had less need for b_2-agonists compared with placebo (6,30).

Hasegawa et al, comparing the effectiveness of 1-week and 2-week courses of oral prednisolone following a 3-day course of intravenous methylprednisolone, found that a course of systemic steroid therapy lasting more than 10 days may have little benefit in the treatment of asthma exacerbation compared to shorter regimens (59). These results were also confirmed by other studies (6,8,25,60).

A recent small randomized trial compared a 5-day course with a 10-day course of prednisolone 40 mg for the treatment of acute asthma and found that a 5-day course of therapy may be sufficient for the majority of patients (6,8,12,58).

The National Heart, Lung and Blood Institute Guideline recommend, after ED discharge, a 5-to 10-day course of corticosteroid therapy to prevent early relapse; patients also should continue to use inhaled short-acting b_2-adrenergic agonists as needed (3,5).

Nonadherence to corticosteroid therapy is surprisingly common (about 50%) in patients discharged from the ED after initial therapy for acute asthma and is one of the main factors associated with relapse (8).

Intramuscular depot injections of corticosteroids may be considered as an alternative to oral route for patients who are at high risk of nonadherence; 12 mg intramuscular betamethasone was safe and as efficacious as prednisone in preventing the relapse of acute asthma (3,8,32,61,62).

Tapering or not tapering the corticosteroid therapy?

Compared with shorter fixed-dose regimens, tapering regimens of corticosteroids offer the theoretic advantage of minimizing the risks of suppressed hypothalamic-pituitary-adrenal axis, worsening airway inflammation, and relapse when corticosteroids are discontinued (1-5,8). Nevertheless the risk of corticosteroid-related adverse effects and non-adherence to therapy may increase, because for the patients the slowly tapering regimens tend to be longer and more complicated than fixed-dose regimens (1-4,8,32,63).

Two recent randomized clinical trials compared the difference in early relapse rates and adrenal suppression between patients receiving an 8-day course of 40 mg/day prednisolone and those receiving an 8-day tapering course of prednisolone. No significant differences between groups in FEV_1% predicted, adrenal suppression, or rates of relapse at day 12 or 21 after discharge were present (5,8,63,64).

Furthermore no patients had evidence of adrenal suppression from either dosing regimen (63).

Tapering oral glucocorticoids is not necessary if the duration of treatment is less than three weeks (a duration too brief to cause adrenal atrophy) and if inhaled steroids are concomitantly prescribed for ongoing therapy (to prevent relapse) (1-6,8,27,32,63,64).

What to do in pregnancy?

Pregnancy may affect the course of asthma and asthma may affect pregnancy outcomes. Uncontrolled asthma is associated with many maternal and fetal complications, including hyperemesis, hypertension, pre-eclampsia, vaginal haemorrhage, intrauterine growth restriction, preterm birth, increased perinatal mortality, and neonatal hypoxia; on the contrary, if asthma is well controlled throughout pregnancy little or no increased risk of adverse maternal or fetal complications is present (1,3,65).

The management of acute asthma in pregnancy may be affected by concerns about harmful effects of medications on the fetus, but the maternal and fetal risks of uncontrolled asthma are much greater than the risks from using conventional asthma medications.

The GINA and British guidelines recommend that drugs therapy should be given as for a non-pregnant patient with acute asthma, including repeated doses of inhaled b_2-agonists and early administration of steroid tablets (3,65).

Continuous fetal monitoring should be performed when asthma is uncontrolled or severe, or when fetal assessment on admission is not reassuring (3).

Inhaled corticosteroid in acute setting

Inhaled corticosteroids (ICS) are the cornerstone of long term therapy in severe asthma. However, they have been considered ineffective in the treatment of acute exacerbations of asthma (10,28).

The British guidelines, that in the 1995 edition recommended to double the dose of inhaled corticosteroids when asthma control deteriorate, in the latest 2008 version recognised the absence of evidence for the use of inhaled steroids as alternative or additional treatment to steroid tablets/venous for acute asthma; further randomised trials are required to determine the role of inhaled steroids in these patients (2).

The most important asthma guidelines support that inhaled steroids do not provide benefit in addition to the initial treatment, but should be continued, or started as soon as possible, to start the chronic asthma management plan (1-4).

Rodrigo et al. suggested that ICS have early beneficial effects (1 to 2 hours) when they were used in multiple doses administered in time intervals < 30 min over 90 to 120 min. They also demonstrated that the use of repeated doses of inhaled fluticasone (3,000 mcg/hour administered through a metered-dose inhaler and spacer at 10-minute intervals for 3 hours) was more effective than intravenous hydrocortisone (500 mg) and was associated with an early improvement, particularly in those patients with the most severe obstruction (10,12,66).

The rapid response (minutes) is one of the strongest pieces of evidence in favour of a nongenomic effect; the evidence suggests that inhaled steroids decrease airway blood flow by modulating sympathetic control of vascular tone, potentiating noradrenergic neurotransmission in the airway vasculature (10,43,47,67-73).

Potential advantages of ICS in acute asthma therapy might include lower systemic side effects, direct delivery to the airways, and greater efficacy in reducing airway reactivity and edema either alone or in addition to CS, especially in patient with prolonged duration of symptoms before the ED presentation and poor response to treatment (12,31,33,44-46,49,74,75).

In a recent Cochrane review, Edmonds et al. suggest that there is insufficient evidence that ICS alone is as effective as systemic corticosteroids (11,31,49,60,76-78).

The evidences do not support the use of inhaled corticosteroids as a substitute for systemic corticosteroids in the ED; inhaled corticosteroids are, however, preferred for long-term asthma control (5). Further research is needed to clarify whether ICS therapy should be employed in acute asthma treatment in the ED or following ED discharge (49).

Additional issues

To reduce the frequency and severity of exacerbations in severe asthma, management and follow-up

requires greater attention. Severe asthma is a heterogeneous condition in terms of pathophysiology, associated co-morbidities, and significant social and psychological impacts. These factors lead to high exacerbation rates. Consequently, a different management approach is needed to address these issues. Understanding and managing the heterogeneity in severe asthma is now recognized as the major challenge for this disease (79). One option is multi-dimensional assessment and intervention. This approach, also termed as 'care bundles', is similar to those used in cardiology for myocardial infarction and the management of elderly people with co-morbidities. For severe asthma, assessment and intervention domains need to focus on several key components

- Behavioural: the optimization of asthma management skills through education programmes that include prescription and translation of written asthma action plans,
- Risk factors: the reduction of risk factors with interventions such as intensive smoking cessation, weight management programmes, and effective management of triggers,
- Airway: optimal pharmacotherapy,
- Co-morbidity: management using guideline based care.

The approach of multi-dimensional assessment and individualized management has been designed for asthma (80), adapted to severe asthma (81) and tested in older people with asthma and COPD where it has proven to be effective. This approach resulted in major improvements in both quality of life and biological outcomes (82). This approach can be initiated during any of the exacerbation phases.

Conclusions

Acute severe asthma is a medical emergency that should be immediately treated. Bronchodilators (b2-agonists) and anti-inflammatory medications (systemic corticosteroids) are first-line agents for acute asthma.

The early use of systemic corticosteroids within 90 minutes of presentation to ED significantly reduces admission rates, leads to quicker resolution and reduces relapses for most patients with exacerbations, especially those who have severe asthma and who have not a rapid response to initial therapy with an inhaled $beta_2$-adrenergic agonist. The evidence supports that oral corticosteroids are as effective as those parenterally administered. It seems reasonable to select oral agents as the first-line choice while reserving intravenous corticosteroids for individuals who are unable to swallow, obtunded or intubated or do not tolerate oral medications.

High doses of corticosteroids offer no further benefit over low dose in patients with acute severe asthma (40-50 mg of prednisolone or 400 mg daily parenteral hydrocortisone for adult, 20 mg prednisolone for children aged 2-5 years, 30-40 mg for children >5 years and 10 mg of soluble prednisolone for children aged less than 2 years, intravenous hydrocortisone 4 mg/Kg repeated every 4 hours for severely affected children who are unable to retain oral medication).

The guidelines recommend, after ED discharge, a 5-to-10-day course of oral corticosteroid therapy to reduce the high risk of early relapse.

Uncontrolled asthma in pregnancy is associated with many maternal and fetal complications, for this reason drug therapy should be given as for a non-pregnant patient with acute severe asthma, including repeated doses of inhaled $beta_2$-agonists and early administration of steroid tablets.

Tapering oral glucocorticoids is not necessary if the duration of treatment is less than three weeks, a duration too brief to cause adrenal atrophy.

Exacerbations, are a common problem in severe asthma. They are multi-component events that are associated with an increased risk of future exacerbations and accelerated decline in lung function. Research is needed to better define the recognition, mechanisms, and management of severe asthma exacerbations. Current clinical care can be optimized by addressing airway pharmacotherapy, self-management skills, triggers and risk factors, and co-morbid diseases that impact on the outcome of severe asthma.

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