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Review on: Use of Systemic Corticosteroids in Asthma

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A B S T R A C T

Systemic corticosteroid use to manage uncontrolled asthma and its associated healthcare burden may account for important health-related adverse effects. We conducted a systematic literature review to investigate the real-world extent and burden of systemic corticosteroid use in asthma. We searched MEDLINE and Embase databases to identify English-language articles published in 2010–2017, using search terms for asthma with keywords for oral corticosteroids and systemic corticosteroids. Observational studies, prescription database analyses, economic analyses, and surveys on oral/systemic corticosteroid use in children (>5 yr old), adolescents (12–17 yr old), and adults with asthma were included. We identified and reviewed 387 full-text articles, and our review included data from 139 studies. The included studies were conducted in Europe, North America, and Asia. Overall, oral/systemic corticoster. Compared with no use, long-term and repeated short-term oral/systemic corticosteroid use were associated with an increased risk of acute and chronic adverse events, even when doses were comparatively low. Greater oral/systemic corticosteroid exposure was also associated with increased costs and healthcare resource use. This review provides a comprehensive overview of oral/systemic corticosteroid use and associated adverse events for patients with all degrees of asthma severity and exposure duration

Keywords: Asthma, systemic corticosteroid, adverse event.

Introduction

Asthma is a chronic respiratory disease that is prevalent worldwide. It is considered as a major cause of morbidity and a main contributor to the high health care expenditure especiall in developed countries.1There are two major pathological features in asthmatics' airways, inflammation, and hyperresponsiveness. These features are interrelated, but not totally dependent on each other.2Airway inflammatory changes include increased airway mucus secretions, airway wall edema, inflammatory cellular infiltrates, epithelial cell damage, smooth muscle hypertrophy, and submucosal fibrosis.3The cellular infiltrates are mainly composed of eosinophils, neutrophils, mast Hicells, lymphocytes, basophils, and macrophages The treatment of asthma has changed considerably over the past two decades.

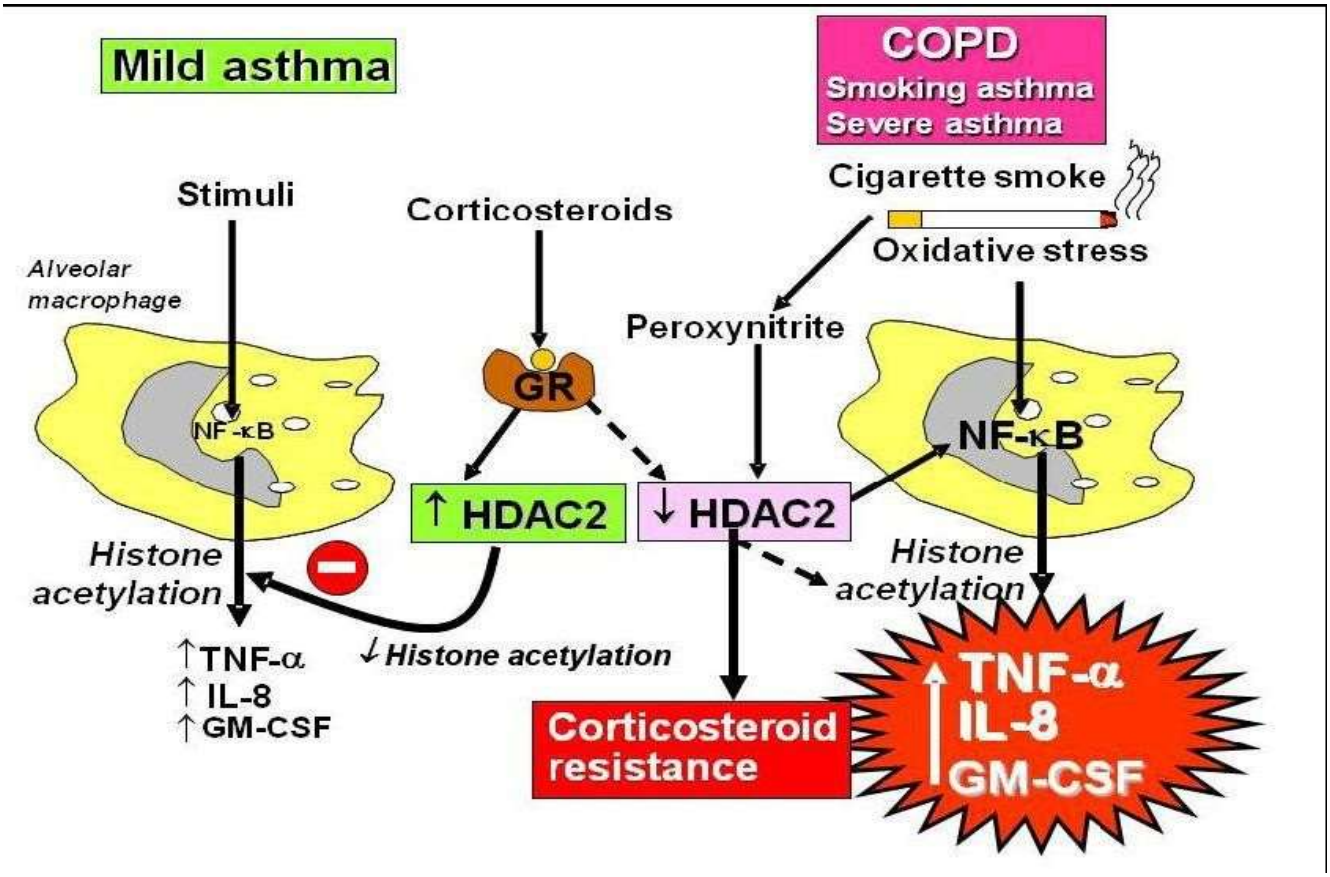
The emphasis has moved from the use of bronchodilator reliever type therapy to the earlier use of anti-inflammatory drugs and in particular inhaled corticosteroids. It is now recognised that bronchial mucosal inflammation and subsequent mediator release are the key processes involved in the pathophysiology of asthma. In particular, recent advances have been made in terms of our understanding of the different cells and inflammatory mediators involved in asthma and also of the neural.

In 2015, asthma was listed as the most prevalent chronic respiratory disease in the world, affecting approximately 358 million people. It is likely that much of the burden associated with this disease is preventable or treatable with appropriate clinical and therapeutic interventionsSince their efficacy in asthma was first described in the 1950s , use of systemic corticosteroids (SCS) in the management of this disease has become widespread. SCS are frequently prescribed in chronic airway diseases as both short- and long-term treatment options . Short-course SCS are a very effective and fast-acting option for the resolution of acute asthma symptoms including exacerbations. Early administration of SCS for the treatment of severe asthma exacerbations is considered a standard of care and is recommended worldwide to be given to the patient within 1 h of presentation. The Global Initiative for Asthma (GINA) recommends SCS for short-term (usually 5−7 days) treatment of severe acute exacerbations. This represents an appropriate use of SCS.Highly accessible and available over the counter in some countries, SCS are prescribed as rescue medication and are largely self-administered at home. It is noteworthy that SCS courses are used to treat not only severe, but also moderate and even mild exacerbations and symptoms .

While we recognise the obvious importance and effectiveness of SCS during asthma-related acuity, we also heed the importance of reducing the inappropriate use of SCS, as this can lead to potential deleterious effects. Thus, this article aims to raise awareness among the medical community of the potential side-effects associated with use of short courses of SCS in patients with asthma of any severity, as well as suggesting strategies to ensure their appropriate use. Inhaled corticosteroids (ICS, also known as glucocorticosteroids, glucocorticoids, steroids) are by far the most effective controllers used in the treatment of asthma and the only drugs that can effectively suppress the characteristic inflammation in asthmatic airways, even in very low doses. By contrast, ICS are largely ineffective in suppressing pulmonary inflammation in COPD and have a poor clinical effect. In both asthma and COPD ICS are commonly given as combination inhalers with long-actinagonists.

1. Etiology of Asthma

Asthma is the most common noncommunicable disease in children, and among the most common in adults. The great majority of people with asthma live in low and middle income countries (LMICs), which have disproportionately high asthma-related morbidity and mortality. Essential inhaled medications, particularly those containing inhaled corticosteroids (ICS), are often unavailable or unaffordable, and this explains much of the global burden of preventable asthma morbidity and mortality. Guidelines developed for LMICs are generally based on the outdated assumption that patients with asthma symptoms <1–3 times per week do not need (or benefit from) ICS. Even when ICS are prescribed, many patients manage their asthma with oral or inhaled short-acting β2-agonists (SABA) alone, owing to issues of availability and affordability. A single ICS–formoterol inhaler-based approach to asthma management for all severities of asthma, from mild to severe, starting at diagnosis, might overcome SABA overuse/over-reliance and reduce the burden of symptoms and severe exacerbations. However, ICS–formoterol inhalers are currently very poorly available or unaffordable in LMICs. There is a pressing need for pragmatic clinical trial evidence of the feasibility and cost-effectiveness of this and other strategies to improve asthma care in these countries. The global health inequality in asthma care that deprives so many children, adolescents and adults of healthy lives and puts them at increased risk of death, despite the availability of highly effective therapeutic approaches, is unacceptable



A World Health Assembly Resolution on universal access to affordable and effective asthma care is needed to focus attention and investment on addressing this need.

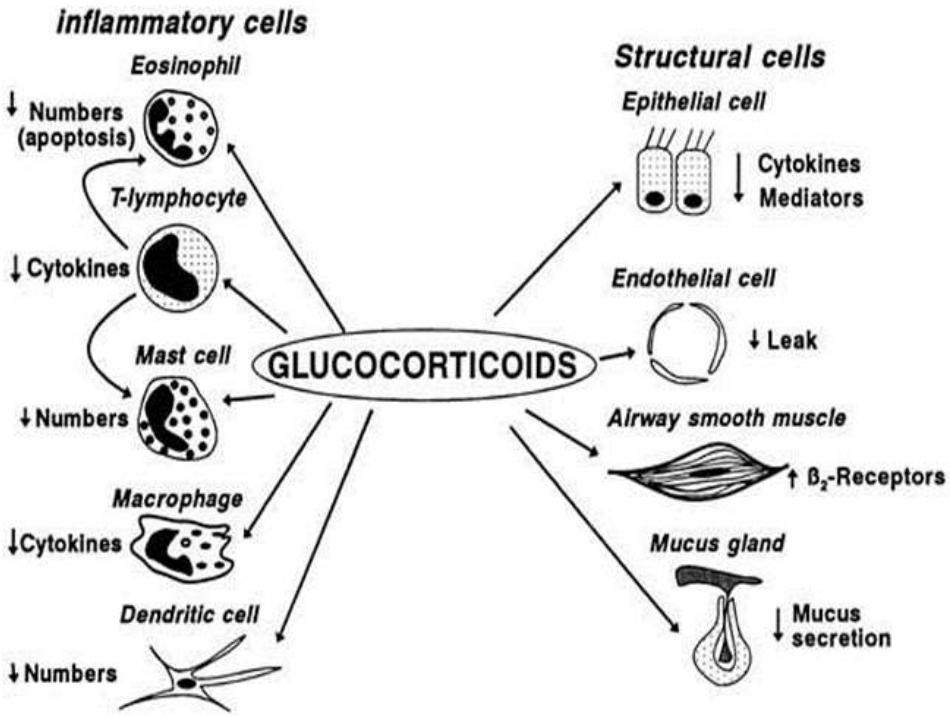
The management of difficult-to-control asthma remains a significant challenge, which frequently requires the input of the wider multidisciplinary team.

This review covers the importance of systematic assessment, phenotyping, treatment options at step 4, an overview of biologics and novel therapies for type 2 (T2) inflammation, and nonpharmacological interventions. Once people have been identified as suffering from difficult-to-control asthma, it is important to use the systematic assessment process to allow accurate diagnosis and optimization of adherence as well as identification and treatment of any relevant comorbidities. Before initiating a biologic, it is important to optimize inhaled therapies and sufficiently phenotype individual patients to allow for the logical use of biologic agents targeting T2 inflammation.

For patients who either do not have evidence of T2 inflammation or remain symptomatic despite biologics, attention should be paid to the available nonpharmacological interventions. Difficult-to-treat asthma remains an area of significant unmet need, but improvements in models of service delivery and the ongoing pharmacological pipeline are causes for significant optimism that sooner rather than later there will no longer be asthmatic patients who are difficult to treat.

2. Systemic corticosteroids :

Systemic corticosteroids given early in the course of treatment of acute asthma exacerbations in the ED were overall shown to be effective and are recommended by different asthma guidelines like GINA and EPR3. Littenberg and Gluck initially showed that they decrease hospital admission rate. Five subsequent studies had, however, conflicting results. Rodrigo and Rodrigo reviewed all these six studies and concluded that there was no improvement in hospital admission rate or lung function. They, however, reported a trend of improvement in lung function only with medium or high doses systemic corticosteroids. Hence, data in terms of lung function are more encouraging.] In terms of effect on exacerbation relapse after discharge from the ED, most studies showed less relapse with systemic corticosteroid although others did not. One important issue with all these studies is the low number of recruited patients. Almost all had subject number <100 per study and all were performed in adults. On the other hand, Krishnan *et al*. recently reviewed nine published studies on the use of systemic corticosteroids in acute asthma in adults and concluded "systemic corticosteroids provide clinically meaningful benefits in patients presenting with acute asthma." In children, more limited data showed benefit of systemic steroids used early in the ED with decreased rate of admission. A Cochrane database review by Rowe *et al*. showed decrease rate of admission in patients with acute asthma with the use of systemic corticosteroids in adults and children, especially those with severe asthma and those not currently receiving steroids.

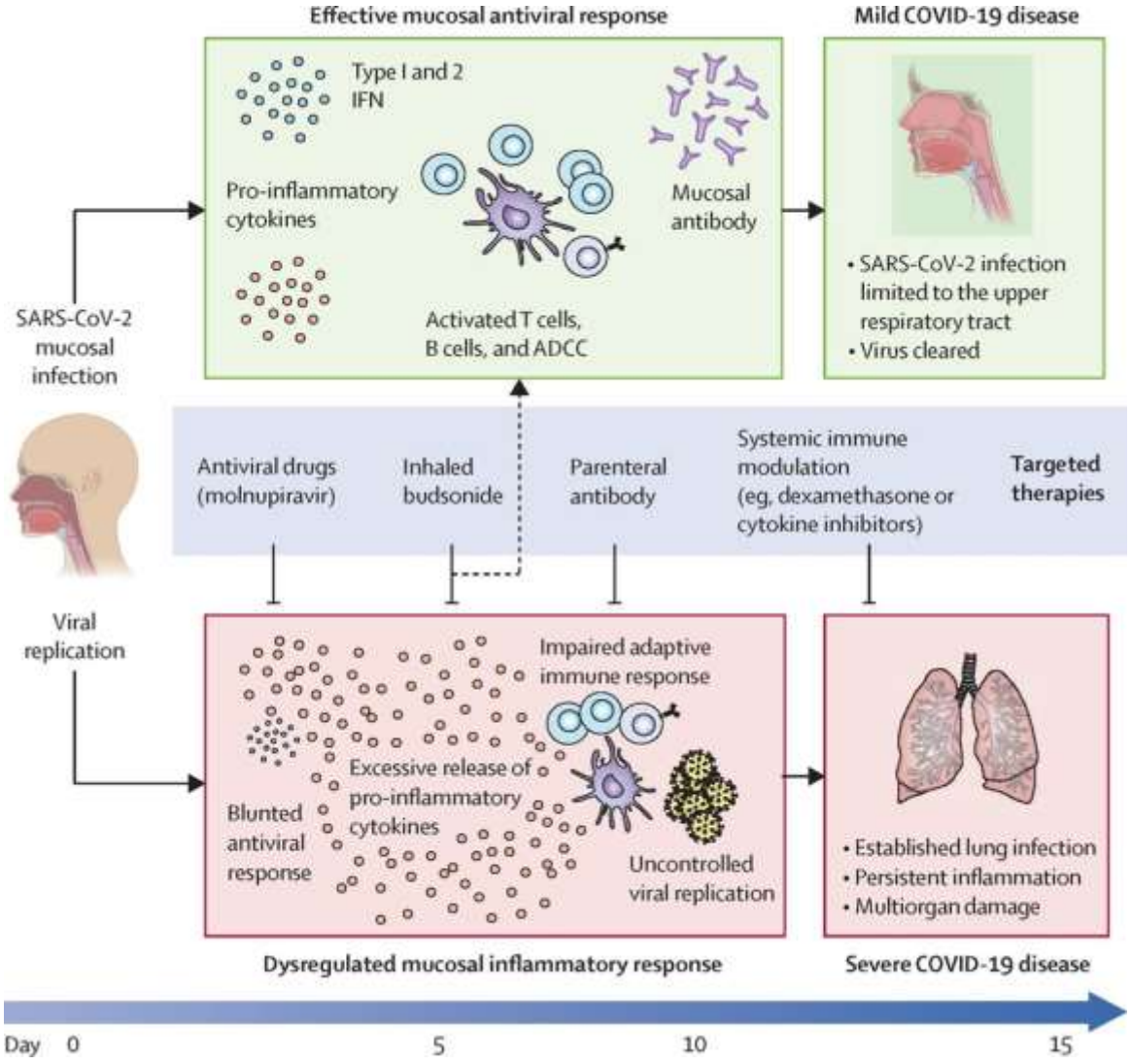


Studies also showed no difference in the efficacy or onset of action between oral and IV administration. Fifty-two adults with severe acute asthma were treated with either IV hydrocortisone or prednisolone. There was no difference in their peak flow measurements 24 h after admission. Ratto *et al*. compared four different doses of methylprednisolone; 160 or 320 mg given orally, or 500 or 1000 mg given IV in four divided doses in adults with acute asthma and found no difference in their forced expiratory volume in 1st second (FEV1) measurements or length of hospitalization. In children also, oral prednisolone was found equivalent to IV methylprednisolone in regards to patients' length of hospital stay.] In addition, oral treatment was more cost-effective. GINA and the EPR3 guidelines prefer oral administration because it is less invasive except in patients with absorption problems or those who are not able to take orally due to the severity of their respiratory distress or because they are vomiting.

Prescribing a short course of oral corticosteroids following the ED treatment of acute asthma exacerbations was found to reduce the rate of relapse. However, courses longer than 5 days were not found to provide any additional benefit. In children, a single dose of dexamethasone

0.6 mg/kg (maximum 18 mg) was found to be equivalent to prednisolone 2 mg/kg/d in two divided doses for 5 days in terms of symptoms resolution. There is also no benefit from using a dose taper over fixed-dose regimen. Due to poor compliance on oral prednisone after discharge from the emergency, intramuscular injection of methylprednisolone was studied as an alternative but was not found superior, plus there was an evidence of injection-site adverse reactions like pain and bruising.

3. Inhaled corticosteroids:



The use of ICS in the treatment of acute asthma was studied in four contexts:

- In comparison to placebo,
- In comparison to systemic corticosteroids,

As add on therapy to systemic steroids with continuation after discharge from the ED

In the first context, a systematic review that looked at eight randomized and blinded studies comparing the efficacy of ICS to placebo in acute asthma exacerbation suggested that ICS are superior to placebo especially when given at high doses (>1 mg of budesonide or fluticasone) and to patients with severe exacerbations. It is important to note that those studies were quite heterogeneous in terms of the severity of asthma in recruited patients, the dose and frequency of ICS administered, and in their outcome measures that included clinical symptoms, pulmonary function, oxygen saturation, admission rate, or relapse rate. In addition, a recent study found that preemptive use of high dose fluticasone (750 mcg BID) at the onset of an upper respiratory tract infection in children with recurrent virus induced wheezing and continuing it for 10 days, reduced the use of rescue oral corticosteroids.

When ICSs were compared with systemic corticosteroids in randomized and blinded studies the conclusions were conflicting. Some studies reported superiority of systemic steroids in reducing admission rate, some reported equal efficacy in relation to admission rate as well, and some reported superiority of ICS. A major study compared high dose fluticasone in the ED and for 5 days post discharge to systemic corticosteroids in the same period in patients with mild to moderate asthma found that oral prednisolone lead to faster improvement in FEV1 at 4 h in the ED and less relapse rate at 48 h post discharge. One recent study showed that in patients who were given systemic corticosteroids plus ICS post discharge from the ED, stopping the systemic corticosteroids after 1 week resulted in rebound in the level of patients' exhaled nitric oxide 2 weeks post discharge despite continuing ICS with no effect on the use of rescue medications or on FEV1.GINA guidelines state that “ICS are effective as part of therapy for asthma exacerbations… and can be as effective as oral corticosteroids at preventing relapses,” while the EPR3 guidelines state that “high doses of ICS may be considered in the ED, although current evidence is insufficient to permit conclusions about using ICS rather than oral systemic corticosteroids in the ED.”

Inhaled corticosteroids were also used as add on therapy to systemic corticosteroids in the ED and continued after discharge. In this context, Rowe *et al*. found a decrease in relapse rate when 1600 mcg/day budesonide for 21 days was added to a 7-day course of 50 mg/day prednisone as compared with placebo. On the other hand, Brenner *et al*. found no difference in the peak expiratory flow rate (PEFR) between high dose flunisolide used for 24 days added to a 5-day course of prednisone 40 mg/day as compared with placebo. A systematic review of 12 trials concluded no benefit of adding inhaled to systemic corticosteroids in reducing the relapse rate of acute asthma.

There are few randomized and blinded studies examining only the short-term effect of ICS in the ED as add on therapy to systemic corticosteroids plus other standard acute asthma therapy. One study looked at the addition of high dose beclomethasone versus placebo to methylprednisolone in 60 adults and found no difference in FEV1 or symptoms between the two groups._ Another study looked at the addition of budesonide nebulizations to methylprednisolone in a population of 26 children with moderate asthma and found no difference in the primary outcome of pulmonary index score, but there was an improvement in the PEFR in the budesonide group compared to placebo. However, the patient number included was very small and PEFR is generally not reliable in young children. The two other randomized and blinded studies that were larger and more rigorous examined the effect of adding 2 mg of budesonide nebulization to prednisone in children with moderate to severe asthma. In the study by Sung *et al*., 44 children with moderate to severe asthma were included. Both groups had no difference in the pulmonary index score. In the other study by Upham *et al*., 180 children with moderate to severe asthma were included. There was no difference in the asthma score at 2 h after intervention or in the admission rate or time to discharge from the ED between the two groups. Collectively, it was hard to come up with a conclusion from these studies about whether adding ICS to systemic steroids in standard acute asthma therapy will add more benefit or not. In addition, the number of subjects recruited by these studies was very small and would not allow subgroup analysis. Therefore, we recently performed a larger blinded and randomized study to look at this question. We found that there was no added benefit of budesonide nebulization (1500 mcg) in the treatment of moderate to severe acute asthma in 2-12 year old children. However, when we looked at only the subgroup with severe acute asthma, budesonide was able to significantly decrease the admission rate of those patients and to lower their asthma score, suggesting an added value. More large trials specifically targeting patients with severe acute asthma are clearly needed.

4. Use of SCS in asthma management

SCS exert an anti-inflammatory effect in asthmatic airways by inhibiting the production of potent pro-inflammatory mediators and by reducing the chemotaxis of inflammatory cells to the lungs . Possibly because of their efficacy, relative affordability or a perception that short courses are harmless, substantial over-prescribing of SCS has been reported in both adults and children with asthma Emergency SCS are prescribed as part of asthma self-management plans for patients at risk of exacerbations ; when not correctly implemented, this may lead to incorrect use of the medication, putting patients at risk of adverse events.

Meanwhile, over-prescription of SCS may be an indicator of poor asthma control which can result from many factors, including poor adherence to inhaled medication (inhaled corticosteroids; ICS) and incorrect use of inhalers. In addition, patients with asthma may use SCS not only for asthma but also for frequently associated comorbidities that present as flaring-up diseases, for example rhinosinusitis with/without nasal polyps, atopic dermatitis, urticaria and conjunctivitis. SCS are widely prescribed for a variety of conditions, even where there is a lack of supporting evidence for their use . An analysis of US national claims data found that more than one in five adults received at least one outpatient prescription for short- term (<30 days) SCS over a 3-year period . This suggests that SCS are seen by prescribers as an effective and cheap option, viewed as low-risk or “benign” medications. Patients with asthma often take SCS in addition to medium- or high-dose ICS, and sometimes also nasal corticosteroids, all of which are known to have systemic bioavailability. Cumulative side- effects of ICS use have been documented . and, therefore, patients taking both ICS and SCS may be at extra risk of steroid-related side-effects.

A recently published systematic review and meta-analysis by MAIJERS *et al*. found that the SCS-sparing effect of high-dose ICS is mostly due to systemic effects. Based on the dose equivalence for effects on adrenal function, the authors of the review suggest that 1000 µg fluticasone propionate has similar systemic effects to 5 mg prednisone], and that 2500 µg budesonide has similar systemic effects to 5 mg prednisone . It has been suggested that high doses of ICS should potentially be considered as harmful as low doses of SCS and that they are accumulative on top of SCS.

The many systemic effects associated with long-term SCS use are well studied and described. The most common serious SCS-associated comorbidities include osteoporosis and osteopenia, type II diabetes, obesity, cardiovascular disorders and adrenal suppression. In addition, use of SCS has been associated with psychiatric symptoms such as insomnia, mania, anxiety or aggressive behaviour, dyspeptic disorder, hypertension, dyslipidaemia, infections, muscle atrophy, cataracts, glaucoma, bruising, change in physical appearance, skin striae and change in appetite .

Although the harmful side-effects of long-term use of SCS are widely known, there seems to be a perception in the medical community that short courses of SCS are safe provided they are used intermittently, rather than continuously. A nationwide cohort study in France reported that 59% of patients with severe asthma were treated with SCS in 2012, with an average frequency of 3.3 courses per patient in the year .

Respiratory diseases are the most frequent indication for short-, medium- and long-term use of SCS, with a considerably higher frequency than other inflammatory conditions and account for approximately 40% of total SCS prescriptions .

There are risks associated with short-term intermittent use of SCS, as well as with longer- term use . A recent report estimated that 93% of patients with severe asthma had at least one condition related to SCS exposure . This includes morbidity and, more importantly, mortality. Regular SCS use is associated with greater all-cause mortality compared with non- SCS use . A nationwide asthma cohort study in Sweden found that patients with asthma who had regular SCS use had a 1.34-fold greater risk of death than those who did not

Side effect of corticosteroid:

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Check with your doctor immediately if any of the following side effects occur:

Rare

- Shortness of breath, troubled breathing, tightness in chest, or wheezing
- Signs of hypersensitivity reactions, such as swelling of face, lips, or eyelids Check with your doctor as soon as possible if any of the following side effects occur:

Less common

- Burning or pain while urinating, blood in urine, or frequent urge to urinate
- Chest pain
- Creamy white, curd-like patches in the mouth or throat and/or pain when eating or swallowing
- Dizziness or sense of constant movement or surroundings
- General feeling of discomfort or illness
- Irregular or fast heartbeat
- Itching, rash, or hives
- Sinus problems
- Stomach or abdominal pain
- Swelling of fingers, ankles, feet, or lower legs
- Unusual tiredness or weakness
- Weight gain

Conclusion

Corticosteroids play an important role in the treatment of acute asthma exacerbations in the ED as well as post discharge from the ED. Further research is greatly needed to shed more light on the use of ICS in those patients, their optimal dose and duration, as well as their concomitant use with systemic corticosteroids. In addition, more research is needed on the safety of dispensing oral corticosteroids for home use in case of asthma exacerbation. The key treatments for asthma are steroids and other anti-inflammatory drugs. These asthma drugs both help to control asthma and prevent asthma attacks. Steroids and other anti-inflammatory drugs work by reducing inflammation, swelling, and mucus production in the airways of a person with asthma. As a result, the airways are less inflamed and less likely to react to asthma triggers, allowing people with symptoms of asthma to have better control over their condition.

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