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Steroids in Asthma: Friend or Foe

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Additional information is available at the end of the chapter

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1. Introduction

Asthma is a common chronic inflammatory disease of the respiratory tract characterized by episodic exacerbations with a heterogeneous population distribution. The prevalence of asthma has increased substantially over the past 5 decades throughout the globe, yet the reasons for this increase remain unknown. The disease represents a substantial burden, not only in terms of morbidity, mortality and reduced quality of life of patients, but also imposing a huge cost on the healthcare facilities in all countries.

2. Burden of asthma

Approximately 300 million people worldwide currently have asthma, and its prevalence increases by 50% every decade, seeing a rise to 400 million by year 2025 (Braman, 2006; Masoli et al., 2004). The increasing number of hospital admissions for asthma, which are most pronounced in young children, reflect an increase in severe asthma, poor disease management, and poverty. Worldwide, approximately 180,000 deaths annually are attributable to asthma. Most asthma deaths occur in those >45 years old and are largely preventable, frequently being related to inadequate long-term medical care or delays in obtaining medical help during the attack.

The financial burden on patients with asthma in different western countries ranges from \$300 to \$1,300 per patient per year, disproportionately affecting those with the most severe disease. It is the most common chronic disorder in children and adolescents, with more than 3 million asthma attacks occurring in more than 5% of all children each year.

Asthma is a cause of concern due to under diagnosis, under investigated, under control and non-adherence to treatment (Barreto, 2006, National Institutes of Health, Bethesda, 2006, Woolcock, 1989, Bassam, 2012). A recent report from WHO suggests that 50% of patients from developed world with chronic diseases do not take their medications as recommended. In developing countries, the situation may be even worse when considering together all the

issues related with poor access to health care, lack of appropriate diagnosis, and limited access to medicines. Poor adherence seriously threatens any effort to tackle such chronic illness (WHO, 2003, Horne, 2003).

Steroids V/S No Steroids in asthma: If ever there was a magic potion that should resolve the symptoms of an affliction, it is the use of glucocorticoids in asthma. Since their first clinical application, there has been uniform agreement that the anti-inflammatory activities of the corticosteroids make them ideal agents to stabilize asthma during all stages of asthma symptomatology ranging from chronic persistent phase to acute severe life threatening exacerbations.

Pathophysiology of asthma: Asthmatic inflammatory process results from inappropriate immune responses to common environmental antigens in a genetically susceptible individual (Wills-Karp 1999). These inappropriate immune responses are orchestrated by a subset of CD4⁺ T helper cells termed T helper 2 (Th2) cells.

Cytokines play a pivotal role in the development of asthma by regulating the expansion of Th2 cells and by mediating many of the Th2 effector functions that underlie the pathogenic events of an asthmatic response. Much effort has recently been placed in elucidating the pathways used by cytokines to mediate their actions. These studies have revealed that cytokine-mediated signals are primarily transduced by the Janus Kinase- Signal Transducer and Activator of Transcription (JAK-STAT) signaling cascade (Darnell, 1997). Recent advances have shown the important roles of JAK-STAT signaling pathway in the pathogenesis of asthma.

3. JAK-STAT signaling in Th1 and Th2 differentiation:

The two major subsets of CD4⁺ T helper cells, Th1 and Th2, secrete mutually distinct profiles of cytokines and thereby coordinate different classes of immune response. The cytokines IL-12 and IL-4 direct the differentiation of Th1 and Th2 cells, respectively, from naive T helper cells. Th1 cells secrete IL-2, IFN- γ , and TNF- β , whereas Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13.

Th1 cells are critically involved in the generation of delayed-type hypersensitivity responses, whereas Th2 cells can direct B cells to mount strong humoral responses. Polarization of immune response toward a Th2 phenotype and when directed against an otherwise innocuous environmental antigen result in the pathogenesis of allergic diseases like asthma.

The Th2 cytokines (IL-4, IL-5, and IL-13) control all the major components that characterize an inflammatory asthmatic response, including IgE isotype switching, mucus production, and the recruitment and activation of eosinophils and have been corroborated by studies in humans. The population of Th2 cells is notably expanded in the airways of asthmatic subjects, and presence of these cells correlates with airway hyper responsiveness (AHR) and airway eosinophilia (Rengarajan et al., 2000, Murphy et al., 2000).

IL-4 and IL-12 activate the Jak-Stat signaling cascade discussed elsewhere in this Perspective series. In this signaling pathway, binding of a cytokine to its receptor leads to the activation of members of the JAK family of receptor associated kinases. These kinases subsequently activate, via tyrosine phosphorylation, preexistent cytoplasmic factors termed Stats (signal transducer and activator of transcription). Tyrosine phosphorylation allows the Stat proteins to dimerize and translocate to the nucleus, where they mediate changes in gene expression by binding specific DNA elements. Although both IL-4 and IL-12 follow this basic signaling framework, the two cytokines differ in the specific Jak and Stat components that they activate (Wurster, A.L. et al 2000). IL-4 stimulates Jak1 and Jak3 to activate Stat6. In contrast, interaction of IL-12 with its receptor leads to the activation of Jak2 and Tyk2 and the subsequent phosphorylation of Stat4. Activation of Stat6 and Stat4 are thus critical events in the signaling cascades of IL-4 and IL-12, respectively.

Mechanism of Action of steroids: Glucocorticoids (GC's) are potent anti-inflammatory agents and are useful in the treatment of both allergic and idiosyncratic asthma. Although the mechanisms of corticosteroid action in asthma are poorly understood, several possible sites of action have been proposed which help reverse the pathologic process of bronchial asthma.

Glucocorticoid receptors (GRs) are specific cytoplasmic transcription factors that mediate the biological actions of corticosteroids (Beato M et al 1995). On ligand binding, GR translocates into the nucleus and binds to DNA at glucocorticoid response elements (GREs) in the promoter region of corticosteroid-responsive genes that induce transcription (Barnes PJ & Adcock IM 1998). GR activation may also influence antiinflammatory events by nongenomic pathways, forming inhibitory interactions within the nucleus with proinflammatory DNA-binding transcription factors, such as activator protein (AP)-1 or nuclear factor (NF)- κ B, or by recruitment of co-repressors, and thereby repressing the actions of these important inflammatory proteins (Karin M. 1998, Ito K et al. 2000). GR nuclear translocation is, therefore, essential and necessary for corticosteroid action.

It has been well investigated that the novel mechanism of GC action is by blocking cytokine signaling via the JAK-STAT signaling pathway. Dexamethasone inhibited IL-2-induced DNA binding, tyrosine phosphorylation, and nuclear translocation of Stat5 in primary T cells. Inhibition of Stat5 correlated with inhibition of expression of IL-2-inducible genes and T cell proliferation. The mechanism of inhibition involved suppression of IL-2 receptor and Jak3 expression. Signaling by IL-4, IL-7, and IL-15, which use IL-2 receptor components, also was inhibited, indicating a block in T cell responses similar to that seen in immunodeficient patients lacking the IL-2 receptor gamma chain or Jak3.

IL-2 signaling also was blocked in patients after treatment with GC's, suggesting that inhibition of cytokine signaling contributes to the clinical efficacy of GC's. Hence inhibition of both cytokine production and Jak- stat signaling contribute to their therapeutic potency (Bianchi, 2000).

Corticosteroids enhance the beta-adrenergic response to relieve the muscle spasm. They also act by reversing the mucosal edema, decreasing vascular permeability by vasoconstriction,

and inhibiting the release of Leukotrienes (LT) LT-C4 and LT-D4. Corticosteroids reduce the mucus secretion by inhibiting the release of secretagogue from macrophages. Corticosteroids inhibit the late phase reaction by inhibiting the inflammatory response and interfering with chemotaxis due to the inhibition of LT-B4 release. The eosinopenic effect of corticosteroids may help to prevent the cytotoxic effect of the major basic protein and other inflammatory mediators released from eosinophils. Corticosteroids have no effect on the immediate hypersensitivity reaction and have no direct role in bronchial reactivity. By blocking the late reaction, they prevent the increased airway reactivity observed with late bronchial reactions, all of which aid in the resolution of bronchospasm in asthmatic patients (Figure 1)

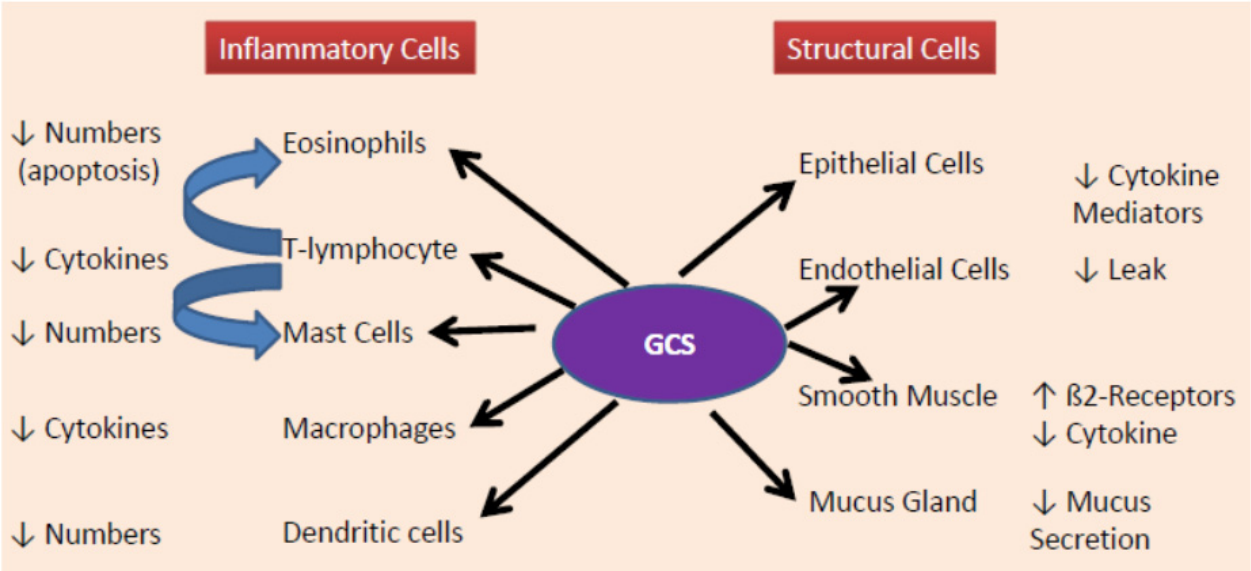


Figure 1. Mechanism of Action of Corticosteroids in asthma

Mode of Delivery: All levels of persistent asthma require daily anti-inflammatory treatment (with additional doses of oral or intravenous steroid based on the severity of symptoms). Inhaled corticosteroids (ICS's) are the safest and most effective anti-inflammatory treatment for patients with persistent asthma of all severity having a significant positive impact on outcomes. Although steroids may be given orally or systemically, and numerous non-steroidal medications are available for treating persistent asthma, ICS's are the treatment of choice considering their risk-benefit and cost-effectiveness ratio. Even when ICS's are given daily over prolong period of time, they have less toxicity than oral or systemic steroids administered only occasionally. A wide range of ICS's are available & the choice depends upon the availability, cost, physician and patient's preference, however it is important to use the equipotent doses of various ICS's while switching over the ICS's for control of asthma (Table-1)

In cases of acute severe asthma or patients requiring maintenance therapy with steroids for chronic persistent asthma intravenous or oral routes are to be preferred, it's important to know the equipotent doses of various type of steroid while starting or switching from one form to another or from one steroids to another in order to get the equivalent response and

to avoid worsening of symptoms (if underdosing done) or side effects (if overdosing done). **Table 2** summarizes the equivalent doses of various types of intravenous or oral steroids. (<http://www.globalrph.com/corticocalc.htm>)

Drug	Low Daily dose (µgm)	Medicium Daily dose (µgm)	High Daily dose (µgm)
Beclomethasone Dipropionate	200-500	500-1000	1000-2000
Budesonide	200-400	400-800	800-1600
Ciclesonide	80-160	10-320	320-1280
Flunisolide	500-1000	1000-2000	>2000
Fluticasone Propionate	100-250	250-500	500-1000
Mometasone Furoate	200	400	800
Triamcinolone acetonide	400-1000	1000-2000	>2000

Table 1. Estimated Equipotent daily doses of all formulations of ICS in adults

Glucocorticoid	Approximate Equivalent dose (mg)	Half-life(Biologic) hours
Short-Acting		
Cortisone	25	8-12
Hydrocortisone	20	8-12
Intermediate-Acting		
Methylprednisolone	4	18-36
Prednisolone/ Prednisone	5	18-36
Triamcinolone	4	18-36
Long-Acting		
Betamethasone	0.6 - 0.75	36-54
Dexamethasone	0.75	36-54

Table 2. Estimated Equipotent daily doses of all formulations of glucocorticoids in adults

Steroids in Children: ICS are the first-line therapy for persistent asthma in children. Major safety concerns of long-term ICS therapy in children include suppression of adrenal function and impaired growth and bone development. Dosage, type of inhaler device used, patient technique, and characteristics of the individual drug influence systemic effects of ICS's. Systemic side effects can occur when continuous high-dose treatment is required for severe asthma or when prescribed dosage is excessive and compliance is unusually good.

It is very important to know that uncontrolled or severe asthma adversely affects growth and final adult height in children & no long-term controlled studies have reported any statistically or clinically significant adverse effects on growth of 100-200 µg/ day of ICS's however it may be seen with all ICS's when a high dose is administered for prolonged periods (dose dependent effect). Different age groups seem to differ in their susceptibility to the growth-retarding effects of ICS's, children aged 4 to 10 are more susceptible than

adolescents, however Children with asthma treated with ICS's attain normal adult height (predicted from family members) but at a later age(Pedersen, 2001, Agertoft & Pedersen, 2000,. Sharek, & Bergman 2000). No studies have reported any statistically significant increase in risk of fracture in children taking ICS's.

Oral or systemic steroids increases the risk of fracture in children with a 32 % increase in 4 courses ever, however ICS's are safe in this regard. Controlled longitudinal studies of 2-5 yrs duration and several cross sectional studies found no adverse effect of ICS on bone mineral density (Agertoft & Pedersen , 1998, Hopp et al., 1995).

Suppression of Hypothalamic-pituitary-adrenal (HPA) axis: Though differences exist between the various ICS's and inhaler devices, treatment with ICS's doses of less than 200 µg budesonide or equivalent daily is normally not associated with any significant suppression of the HPA axis in children. At higher doses, small changes in HPA axis function can be detected with sensitive methods. The clinical relevance of these findings is not known, since there have not been reports of adrenal crisis in clinical trials of ICS's in children. However, adrenal crisis has been reported in children treated with excessively high doses of ICS's (Roux et al., 2003).

Recent studies confirm that benefits of ICS, properly prescribed and used, clearly outweigh not only their potential adverse effects but also the risks associated with poorly controlled asthma.

Benefits of oral corticosteroids for asthma include reduction in mucus production, chest tightness, coughing, and wheezing. Other non-asthma related conditions, such as sinus conditions and psoriasis, may also improve due to the anti-inflammatory properties of oral steroids.

Side effects of steroids: Side effects of short-term oral steroids include fluid retention, stomach upset, excessive hunger, and blurred vision. Difficulty concentrating, insomnia, and mood changes can also occur as a result of taking oral corticosteroids. The systemic side-effects of long-term treatment with high doses of ICS's may include cataracts, osteoporosis, easy bruising, and hair loss, Weight gain, an increase in facial hair in women, and muscle weakness. Long term use of oral corticosteroids may also increase the risk of diabetes, high blood pressure, and certain infections. Systemic effects of inhaled glucocorticosteroids are not a problem in adults at doses of ≤ 400 mg budesonide or equivalent daily.

Factors affecting response of ICS's: Three most important factors that appear to have significant impact on the effectiveness of inhaled corticosteroid (ICS) treatment are:

1.) **Patient compliance with inhaled anti-asthma therapy:** The term "Compliance" is defined as the extent to which a patient's behavior matches the prescriber's advice but recently it has mostly been superseded by the term adherence, a similar concept but having fewer negative connotations from physician/patient relationship point of view (Haynes, 1979). Adherence is defined as the extent to which the patient's behavior matches agreed recommendations from the prescriber.

The issue of noncompliance is complicated by different patterns of noncompliance and a variety of measurements of noncompliance. Cochrane GM 1996 identified several patterns of noncompliance, including taking only half of the medications at the prescribed times, taking the medication regularly for a period and stopping, and skipping prescribed doses. Compliance with preventive therapy such as ICSs whose effect is seen over a period of weeks may be less than compliance with drugs that relieve asthma symptoms more rapidly. Patient adherence to medication is influenced by a number of factors relating to how the individual judges the necessity of their treatment relative to their concerns. These factors can be categorized as follows:

1. Treatment factors:
 - Dosing schedule too frequent
 - cost / non-availability of medicine
 - Complexity or inconvenience of treatment regimen
 - Need to use proper inhaler technique
 - Discomfort of drug administration (eg, bad taste, dry throat, hoarseness, fungal infections)
 - Physician's Inertia / Attitude/ lack of communication
 - Proper education about the disease not given by physician
2. Behavioral factors
 - Belief that medication is not really needed (esp. Controller medicine (ICS)
 - Belief that medication would not work
 - Poor perception of the impact of the disease (symptoms, experience, expectations & interpretation of illness)
 - Fear of adverse effects or dependence/ negative orientation to medicines
 - Steroid phobia
 - Forgetting to take medication
 - Volitional non-adherence: voluntarily not taking medication
 - Non-volitional non-adherence: from failure to take medication properly (e.g. ICS± LABA)
3. Contextual issues: Past experiences, Cultural issues/ Social beliefs/ Poor pt /View of others/ Practical difficulties

It is important to keep the medication regimen as simple as possible, prioritize recommendations, educate the patient regarding disease management, and individualized the dosing and schedule of ICS as per patient's requirement.

2.) Inhalation technique. The effectiveness of inhaler therapy depends not only on compliance, but also on the inhaler technique. Various types of inhaler devices are available including trubohaler, discus etc however they can be broadly categorized based on the form of drugs used as dry powder inhalers (DPI) and Metered Dose inhalers (MDI). Although both types of inhalers are equally effective but While prescribing ICS to patient due consideration should be given to the age of the patient, comorbid conditions, coordination between the hands & mouth & the educational level of patient, otherwise the inhaled ICS

will get deposited in the oropharynx & produce local side effects(such as change in voice, Oropharyngeal candidiasis). Use of Spacer with MDI can largely reduce the deposition of the ICS in throat & hence avoid local side effects of the steroids.

3.) **Impact of inhalation technique and device on drug deposition in the lungs:** For ICSs, the efficacy depends on the topical activity of the drug that reaches the target area, whereas the adverse events depend both on oral deposition and systemic activity. Systemic activity of the drug depends on the amount of the drug absorbed either through the GI tract or through the lungs, as well as on the first-pass metabolism for drug absorbed through the GI tract.

The amount of drug delivered to the lungs depends on the inhalation technique,(Dolovich, 1981, Jackson & Lipworth , 1995) as well as on the type of inhaler used and the fine particle size (respirable particle diameter between 1- 4 μm) of the drug. **Table -3** shows the Estimates of the Lung to Systemic Bioavailability Ratios for different types of ICS's.

Product	% Dose Deposited in the Lungs	% Dose Reaching the Systemic Circulation after Absorption from the Gastrointestinal Tract	Lung/Systemic Bioavailability Ratio
BDP via CFC propellant	5.5	14.7	0.27
BDP (non-CFC propellant)	56.1	5.5	0.92
Budesonide via MDI	15	7.7	0.66
Budesonide via DPI	30	5.3	0.85

BDP-beclomethasone dipropionate. CFC-chlorofluorocarbon. MDI-metered-dose inhaler, DPI- dry powder inhaler.

Table 3. Estimates of the Lung to Systemic Bioavailability Ratios for Inhaled Corticosteroids

Recent Recommendations about the delivery device for ICS from American College of Chest Physicians/American College of Asthma, Allergy, and Immunology states that:

1. For the treatment of asthma in the outpatient setting, both the MDI with a spacer/holding chamber and the DPI are appropriate devices for the delivery of ICS's.
2. For outpatient asthma therapy, the selection of an appropriate aerosol delivery device for ICS's includes the patient's ability to use the device correctly, the preferences of the patient for the device, the availability of the drug/device combination, the compatibility between the drug and delivery device, the lack of time or skills to properly instruct the patient in the use of the device or monitor the appropriate use, the cost of therapy, and the potential for reimbursement(Dolovich, 2005). **Table -4** summarizes the advantages & disadvantages of all the devices available for the delivery of ICS's

Type	Advantages	Disadvantages
Small-volume jet nebulizer (Respiratory solution, Respules, nebulers)	Patient coordination not required Effective with tidal breathing High dose possible Dose modification possible Can be used with supplemental oxygen Can deliver combination therapies if compatible	Lack of portability Pressurized gas source required Lengthy treatment time Device cleaning required Contamination possible Not all medication available in solution form Does not aerosolize suspensions well Device preparation required Performance variability Expensive when compressor added
Ultrasonic nebulizer	Patient coordination not required High dose possible Dose modification possible Small dead volume small and portable Faster delivery than jet nebulizer No drug loss during exhalation (breath actuated devices)	Expensive Need for electric power source Contamination possible Not all medication available Device preparation required before treatment Does not nebulize suspensions well Possible drug degradation airway irritation with some drugs
Pressurized MDI (CFC/ HFA as propellant) accuhaler, Evohalers	Portable and compact Treatment time is short No drug preparation required No contamination of contents Dose-dose reproducibility high Some can be used with breath actuated mouthpiece	Coordination of breathing and device actuation needed High pharyngeal deposition Upper limit to unit dose content Remaining doses difficult to determine Potential for abuse Not all medications available
Holding chamber, reverse flow spacer, or spacer (Zerostat, Zerostat-v spacer)	Reduces need for coordination Reduces pharyngeal deposition	Inhalation can be more complex for some patients Can reduce dose available if not used properly More expensive/Less portable Integral actuator devices may alter aerosol properties compared to native actuator
DPI (Turbohaler, Diskus, Rotahaler, Handihaler, aerolizer)	Breath-actuated Less coordination required No Propellant required Small and portable Short treatment time Dose counters	Requires moderate to high inspiratory flow Can result in high pharyngeal deposition Not all medications available

CFC-Chloro-fluor-Carbon, HFA- hydro-fluoro-alkane, MDI- Metered dose inhaler, DPI- Dry Powder inhaler

Table 4. Advantages and Disadvantages of Aerosol-Generating Device or System

In short, effective asthma treatment requires a combination of pharmacology and psychology. Effective prescribing needs to take account of patients’ beliefs, expectations, and adherence behavior.

Goal of Asthma Management: According to Global Initiative for Asthma (GINA 2010) Guidelines issued by the National Heart Lung & Blood institute, the goals for successful management of asthma are to:

- Achieve and maintain control of symptoms
- Maintain normal activity level including exercise
- Maintain pulmonary functions as close to normal as possible
- Prevent asthma exacerbations
- Avoid side effects from asthma medications
- Avoid asthma mortality

Therefore, for successful management of asthma and optimum control of asthma , patients should always be assessed to know their status of asthma control , Following classification of asthma by level of control is more relevant and **useful** (Figure 2).

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV ₁) [‡]	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year*	One in any week [†]

Adopted from Global Initiative for Asthma (GINA 2010) Guidelines

* Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.

† By definition, an exacerbation in any week makes that an uncontrolled asthma week.

‡ Lung function testing is not reliable for children 5 years and younger.

Figure 2. Classification of asthma by level of control

To reach this goal, four interrelated components of therapy are required:

Component 1: Develop patient/doctor partnership: In order to help in the effective management of asthma so that the asthmatic patient can learn how to: avoid risk factors, take medications correctly, understand the difference between “controller” and “reliever” medications, monitor their status using symptoms and, if relevant Peak expiratory Flow (PEF) recognize signs that asthma is worsening and take action, seek medical help as appropriate.

Component 2: Identify and Reduce Exposure to Risk Factors: To improve control of asthma and reduce medication needs, despite physical activity is a common cause of asthma symptoms however patients should not avoid exercise. Common strategies for avoiding allergens and pollutants include the followings; Stay away from tobacco smoke, patients and parents should not smoke, avoid drugs, foods, and additives if they are known to cause symptoms, reduce or, preferably, avoid exposure to occupational sensitizers.

Component 3: Assess, Treat, and Monitor Asthma: Each patient is assigned to one of five treatment “steps” based on the frequency and severity of symptoms, PFT values and the exacerbations. At each treatment step, asthma education, environmental control & vaccination are important component of asthma control. Rescue medication should be provided for quick relief of symptoms as needed. As the severity of disease increases, from Steps 2- 5, patients should be given one or more regular controller medications (ICS) in order to keep asthma under control & to avoid the morbidity & mortality related with asthma and to prevent the long term consequences of the disease. Regular use of ICS has *demonstrated* high efficiency in reducing asthma symptoms, reducing frequency & severity of exacerbations, reducing mortality, improving quality of life, improving lung function, decreasing airway hyper-responsiveness & controlling airway inflammation.

Component 4: Managing asthma exacerbations: Exacerbations of asthma are characterized by episodes of progressive increase in shortness of breath, cough, wheezing or chest tightness, or some combination of these symptoms. Management of asthma exacerbation requires close objective monitoring (both clinical and using PEF), repetitive administration of rapid-acting inhaled bronchodilators, early introduction of systemic glucocorticosteroids and oxygen supplementation. It is very important to use systemic steroids early in case of exacerbation in order to control the underlying inflammation earliest possible. GINA guidelines have simplified the recognition of severity of acute exacerbation of asthma and management in acute care setting base on the severity of symptoms & response to treatment (For details: www.ginasthma.org)

Stepwise approach for asthma Management: GINA guidelines have simplified the management of asthma at all stages in stepwise manner starting from rescue medicines to regular controller medicine. (Figure 3)

4. Glucocorticoid resistance

Although glucocorticoids are highly effective in the control of chronic inflammation or immune dysregulation occurring in asthma pts however a small proportion of patients displays persistent immune activation and airway inflammation and fail to respond despite high doses of oral corticosteroids imposing a big challenge for the physicians. (Barnes, 1995, 1995, Sze'er, 1997). This group of patients has been classified as “steroid-resistant”

Step 1	Step 2	Step 3	Step 4	Step 5
Asthma education Environmental control				
As needed rapid-acting β_2 -agonist	As needed rapid-acting β_2 -agonist			
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2 -agonist	Medium-or high-dose ICS plus long-acting β_2 -agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier**	Medium-or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

* ICS=inhaled glucocorticosteroids
**=Receptor antagonist or synthesis inhibitors

Adopted from Global Initiative for Asthma (GINA 2010) Guidelines

Figure 3. Stepwise approach for asthma Management

Steroid resistant asthma: American Thoracic Society (ATS) defined Steroid resistant patients as characterized by a pre-bronchodilator Force expiratory volume in 1 sec (FEV1) of less than 70% predicted with a maintained bronchodilator response. Steroid resistance is defined by administering a course of oral prednisone e.g. 40 mg/d (divided doses) for 7 days or preferably 2 wk, and observing the effect on morning pre-bronchodilator FEV1 (Lee, 1996). If the FEV1 fails to increase by 15% (and 200 ml), the patient is considered steroid resistant (Sally et al., 2000). These patients show the typical diurnal variability in peak expiratory flow and bronchodilatation with inhaled B-2 agonists. This type of trial can also assess the possibility of poor adherence to the maintenance regimen.

Patients with steroid resistance can be grouped into two broad categories,

Type 1 steroid resistance: is either immune-mediated or acquired as the result of environmental triggers or lifestyle. Clinically, such patients will develop steroid side effects, including adrenal gland suppression, osteoporosis, and cushingoid features from pharmacologic doses of systemic steroids. This is because there is only one (glucocorticoid resistant) GR gene and these patients have steroid resistance only at the level of their immune/inflammatory cells (i.e., T cells). The rest of the tissues in their body remain sensitive to the deleterious effects of systemic steroids.

Type 2 steroid resistances: is rare but involves a generalized primary cortisol resistance that affects all tissues and is likely associated with a mutation in the GR gene or genes that modulate GR function. This form is not associated with the development of steroid’s side effects or suppression of morning cortisol levels (Table 5). It is analogous to genetically inherited familial cortisol resistance. When patients present with a history of no side effects

after high doses of prednisone, it is critical to confirm that they are taking the oral prednisone by checking their morning serum cortisol after a course of therapy under strict supervision. Such individuals need alternative approaches to control their pulmonary inflammation.

Features	Type 1 steroid resistances	Type 2 steroid resistances
AM cortisol levels	Suppressed	No
Cushingoid side effects	Yes	No
Cause	Cytokine induced(May be genetic), Allergy, Microbes	Genetic
GCR ligand and DNA binding affinity	Reduced	Normal
GCR numbers	Normal or High	Low
Reversibility of GCR defect	Yes	No

Table 5. Summarizes difference in both Types of steroid resistance

It is imperative to exclude confounding factors when trying to make the diagnosis of steroid-resistant asthma in a patient. These factors include non-adherence with asthma medication, inadequate inhalation technique, incorrect diagnosis, unrecognized concomitant diagnoses, and ongoing exposure to environmental allergens, abnormal corticosteroid pharmacokinetics, and psychosocial disturbances. Low dose methotrexate, cyclosporine, Intravenous immunoglobulin, leukotriene antagonists, such as zafirlukast and montelukast and Nedocromil sodium has been used in steroid resistant patients with varying success rates and with associated side effects.

5. Clinical features of glucocorticoid-resistant asthma

Glucocorticoid resistance in asthma was first described in six patients with asthma who did not respond clinically to high doses of systemic glucocorticoids and in whom there was also a reduced eosinopenic response (Schwartz et al .,1968). Larger groups of patients with chronic asthma who were glucocorticoid resistant were subsequently identified (Carmichael et al ., 1981). These patients were not Addisonian and did not suffer from the abnormalities in sex hormones described in familial glucocorticoid resistance (see below). Plasma cortisol and adrenal suppression in response to exogenous cortisol is normal (Lane et al., 1996). Complete glucocorticoid resistance in asthma is very rare, but reduced responsiveness is more common, so that oral glucocorticoids are needed to control asthma adequately (steroid-dependent asthma).

Mechanisms of glucocorticoid resistance: There may be several mechanisms for resistance to the effects of glucocorticoids. Although a family history of asthma is more common in patients with GCR than GCS asthma, little is known about its inheritance. It is possible that a certain proportion of the population has glucocorticoid resistance which only becomes manifest when they develop a severe immunological or immune disease that requires glucocorticoid therapy. Resistance to the inflammatory and immune effects of

glucocorticoids should be distinguished from the rare familial glucocorticoid resistance, where there is an abnormality of glucocorticoid binding to GR.

Glucocorticoid resistance may be *primary* (inherited or acquired of unknown cause) or *secondary due to* reduced glucocorticoid responsiveness (glucocorticoids themselves, cytokines, b-adrenergic agonists).

Primary glucocorticoid resistance: There are several possible mechanisms for a reduced anti-inflammatory response to glucocorticoids.

- a. Pharmacokinetic abnormalities.
- b. Antibodies to lipocortin-1.
- c. Cellular abnormalities.
- d. Abnormality in GR function.
- e. Interaction between GR and transcription factors.

Secondary glucocorticoid resistance: various probable mechanisms include:

- a. Down-regulation of GR.
- b. Effects of cytokines.
- c. Effect of B2 agonists.

6. Factors contributing to corticosteroid resistance

A variety of factors known to contribute to immune activation and pulmonary disease have been found to alter corticosteroid responsiveness (**Table 6**).

Clinical allergy and allergen exposure
Infection
Smoking
Obesity
Stress
Ethnicity
Low vitamin D level

Table 6. Factors Contributing to Corticosteroid Insensitivity

6.1. Allergen exposure

Allergen exposure in vivo reduces GR binding affinity in PBMCs from atopic asthmatics. In vitro treatment with cat allergen of peripheral blood mononuclear cell (PBMC) from cat-allergic asthmatics was also observed to reduce GR binding affinity and T-cell proliferation induced by allergens compared with control antigens. The induction of these GR binding abnormalities was found to be IL-2 and IL-4 dependent.

6.2. Infection

Infection is a common trigger for pulmonary disease. An analysis of the T-cell repertoire in patients whose asthma was poorly controlled ($FEV_1 < 75\%$ predicted despite use of high-dose corticosteroids) revealed that their T cells were activated by a microbial superantigen. To determine whether microbial super antigens could alter corticosteroid sensitivity, the capacity of corticosteroids to inhibit the activation of T cells from normal subjects with super antigens as compared with the mitogen, phytohemagglutinin, was studied. While corticosteroids caused a 99% inhibition of phytohemagglutinin-induced PBMC proliferation, there was only 19% inhibition of super antigen-induced T-cell proliferation. The mechanism by which super antigens induce corticosteroid resistance of human T cells is via activation of the Mitogen-Activated protein Kinase Kinase/Extracellular signal-Regulated Kinase (MEKK-ERK) pathway (Li et al., 2004, Goleva et al., 2004). Viruses can also alter response in corticosteroids. In particular, rhinovirus has been reported to reduce GR nuclear translocation and thereby reduce corticosteroid response.

6.3. Neutrophilia

The nature of the inflammatory infiltrate will also determine whether the particular pulmonary disease being treated is likely to resolve with corticosteroid therapy. Pulmonary diseases associated with infiltration of neutrophils are likely to be Steroid resistant. To determine the potential mechanism of corticosteroid resistance in neutrophils, Strickland et al., 2001 examined relative amounts of $GR\alpha$ and $GR\beta$ in freshly isolated neutrophils and observed increased $GR\beta$, but not $GR\alpha$, protein and mRNA expression in neutrophils at baseline and after IL-8 exposure (Strickland et al. 2001). High constitutive expression of $GR\beta$ by neutrophils may provide a mechanism by which these cells escape corticosteroid-induced cell death.

6.4. Other factors contributing to steroid resistance

Other factors contributing to steroid resistance include smoking, stress, obesity, ethnicity, and vitamin D deficiency. In smokers, oxidative stress results in reduced levels of histone deacetylase-2 (Barnes, Adcock, 2009). Stress may induce steroid resistance via multiple mechanisms, including the chronic elevation of the stress hormone, cortisol, which downregulates expression of the GR (Haczku , Panettieri, 2010). The association of steroid resistance with obesity may be related to the systemic inflammation found in this condition, leading to chronic elevation of TNF and mitogen-activated protein kinase (MAPK) activation that causes GR dysfunction (Sutherland et al., 2008) Black patients with asthma have also been found to have reduced steroid responsiveness compared with white asthmatics (Federico, 2005), although the reason for this is not known, but it could be due to a combination of genetic and environmental factors.

Several recent studies on asthmatics have now shown that low vitamin D levels are associated with increased corticosteroid requirements, and there is a potential role for vitamin D in the enhancement of corticosteroid response (Sutherland et al., 2010)

7. Management of corticosteroid resistance

The management of steroid resistant (SR) asthma poses a significant challenge to the clinician. Identification of the SR patient early in the course of illness is important to prevent tissue remodeling and irreversible changes in lung pathology. Definitions of clinical response to steroid therapy will be dictated by the pulmonary disease being treated and time frame for improvement of clinical disease before unacceptable steroid side effects occur. In the case of asthma, clinical studies have suggested that favorable response to inhaled steroids is associated with high levels of exhaled nitric oxide, high bronchodilator response, and a low FEV₁/FVC ratio prior to treatment (Barnes,2008)

A systematic, stepwise approach is important for a successful outcome (Leung and Bloom, 2003). **Table 7** lists factors to be considered in the evaluation of patients with a history of steroid resistance.

Correct diagnosis
Comorbid conditions- rhinosinusitis, congestive heart failure, COPD, Gastro Esophageal reflex
Drug adherence
Drug delivery
Drug interactions causing enhanced metabolism of steroids
Alternative anti-inflammatory therapies

Table 7. Considerations in Treating Steroid Resistance

- Step 1.** Complete Evaluation including history, physical examination, pulmonary function testing, and appropriate laboratory tests to confirm the diagnosis and rule out concomitant medical disorders such as vocal cord dysfunction, Gastroesophageal reflux/aspiration, chronic rhinosinusitis, allergic bronchopulmonary aspergillosis, heart failure, COPD & broncholitis etc.(**Figure 4**)
- Step 2.** Try to find out psychological & social factors including adherence to therapy and take corrective measures for them.
- Step 3.** Observe the inhalational technique of patient, reeducate, reinforce about the proper technique especially in patients requiring high doses of ICS for severe persistent asthma. Spacer devices should be used to maximize ICS dose delivery and reduce adverse effects.
- Step 4.** Strict environmental control at home, in school, and at work including finding the source of allergens & eliminating the same because persistent allergen exposure will increase the symptoms of asthma & reduces steroid responsiveness.
- Step 5.** Search for concomitant bacterial/ mycobacterial/ fungal infection of the tracheobronchial tree especially in patients taking high doses of ICS or chronic oral steroids. Chronic colonization with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*, can trigger airway inflammation in chronic asthmatics and thus poor responsiveness to steroids.

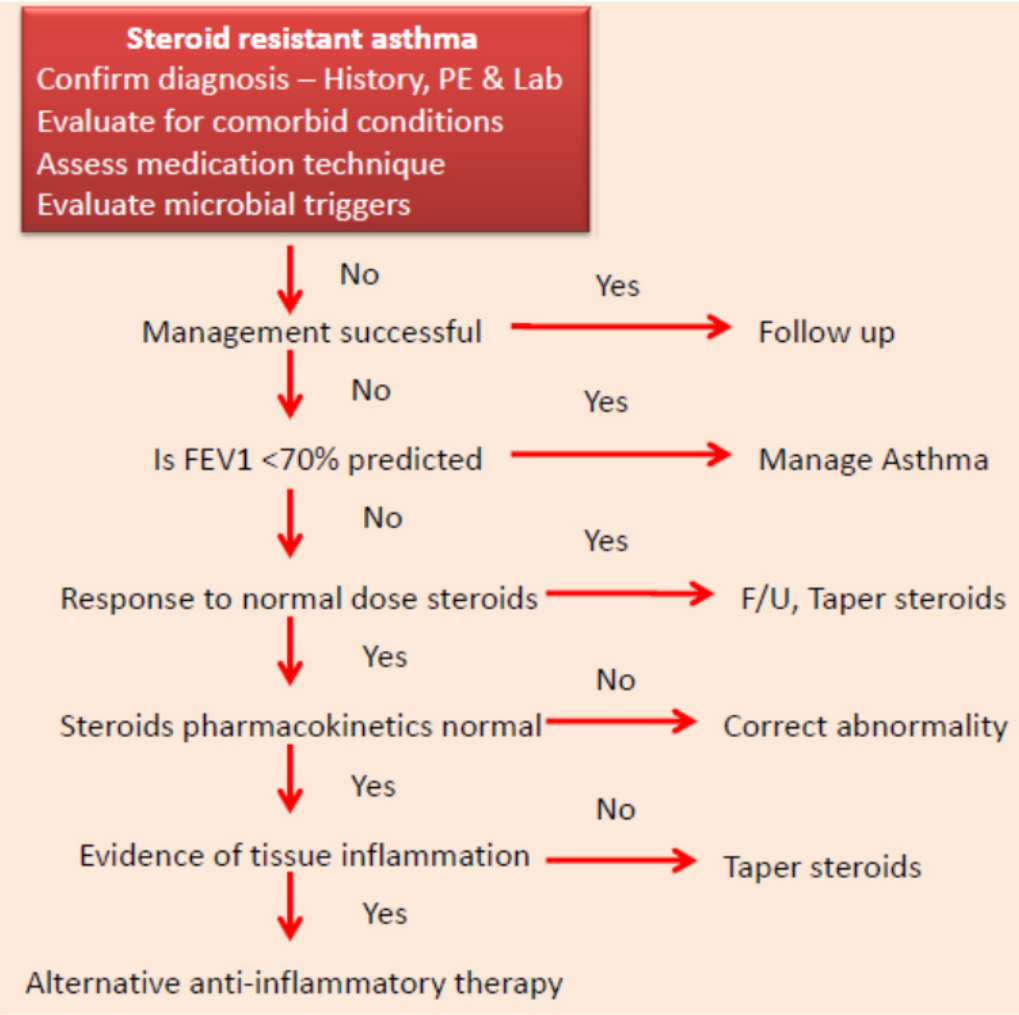


Figure 4. Flow diagram to manage steroid resistant asthma

- Step 6.** Search for factors affecting lifestyle and steroid responsiveness. Patients with Vitamin D deficiency have increased steroid requirements. Other cofactors, including obesity, smoking, no or little exposure to sunlight and pigmented skin are well known to lower vitamin D levels.
- Step 7.** Combination therapy can be used to maximize clinical response. Inhaled long-acting β_2 -agonists (LABA) have been found to enhance Glucocorticoid receptor (GR) nuclear translocation and reduced corticosteroid requirements. Consider addition of other steroid-sparing drugs such as leukotriene modifiers, anticholinergic drugs, nedocromil sodium(Marin, 1996) and theophylline.
- Step 8.** In very difficult case, studies to identify systemic steroid pharmacokinetics and receptors to assess the basis for corticosteroid resistance to determine whether there is incomplete corticosteroid absorption, failure to convert corticosteroids to an active form, or rapid elimination of steroids (frequently as a result of interactions with other medications). Patients with poor absorption of prednisone usually respond well to oral liquid steroid preparations. In patients with rapid corticosteroid elimination, a split dosing regimen (morning & afternoon) is suggested.

Step 9. Consider Steroid sparing anti-inflammatory therapies that would enhance corticosteroid action including cyclosporine (Alexander et al., 1992), IV Immunoglobulin (Mazer , 1991), methotrexate (Mullarkey et al. 1998, Erzurum et al., 1991), mycophenolate mofetil, azathioprine, Macrolides, trolendamycin and gold, depending on the severity of asthma and the potential of significant side effects. Omalizumab (recombinant anti IgE antibody) is useful in patients with primarily allergic asthma & with severe persistent allergic rhinitis.

Further Studies are needed to determine whether cytokine antagonism—TNF- α , IL-2, IL-4, or IL-13—could restore steroid responsiveness because such cytokines have been found to induce steroid resistance. Vitamin D has recently been demonstrated to induce IL-10-producing regulatory T cells (Xystrakis et al., 2006) and enhance steroid action, and may therefore be steroid sparing(Zhang et al., 2010)

8. Novel steroids

Steroids, either systemic or inhaled, are exquisitely active and effective in asthma, but their mechanism of action is broad, and concern for toxicity—even with topical steroids—has limited their wider use. A variety of approaches are being pursued to maximize local activity within the airways and at the same time to minimize systemic absorption and toxicity. One approach is development of on-site-activated steroids such as ciclesonide, which is a nonhalogenated ICS prodrug that requires endogenous cleavage by esterases for activity. Soft steroids are also being developed; these have improved local, topical selectivity and have much less steroid effect outside the target area. They may be inactivated by esterases or other enzymes (for example a lactone–glucocorticosteroid conjugate).

Dissociated glucocorticoids: The recognition that most of the anti-inflammatory effects of glucocorticoids are mediated by repression of transcription factors (transrepression), whereas the endocrine and metabolic effects of steroids are likely to be mediated via glucocorticoid response element binding (transactivation) has led to a search for novel corticosteroids that selectively transrepress, thus reducing the potential risk of systemic side effects. These dissociated steroids which favor monomeric glucocorticoid receptor complexes (i.e., they produce transrepression) and avoid dimerization or transactivation, which is undesirable in asthma would make the treatment of asthma more effective without the current fear of steroid's side effects. Agents from each of these categories are undergoing clinical trials.

Steroid sparing : The combination of long acting beta agonist (LABA) with inhaled corticosteroid (ICS) is used frequently in asthma and a benefit from adding LABA to ICS has been described. One review compared reduced dose (mean 60% reduction in inhaled steroid) ICS/LABA combination to either a fixed moderate/high dose ICS or a reduced/tapering ICS dose. In adults with asthma, who use moderate to high maintenance doses of ICS, the addition of LABA has an ICS-sparing effect. LABA permit a reduction of 37% (253 mcg BDP) in subjects on minimum maintenance ICS and up to 60% (300 mcg FP) in

subjects on maintenance ICS without deterioration in asthma control. They are most effective when combined with ICS, and this combination therapy is the preferred treatment when a medium dose of ICS alone fails to achieve control of asthma (Gibson, 2005). The addition of a LABA to a daily regimen of ICS improves symptom scores, decreases nocturnal symptoms, improves lung function, decreases the use of relief medication, reduces the number of exacerbations and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of ICS, than ICS given alone (Greening, 1994, Pauwel, 1997).

Certain case reports have documented tiotropium as a useful steroid sparing agent however future clinical trials are warranted that explore the use of tiotropium as a potential 'steroid-sparing agent' in severe refractory asthma (Kapoor, 2009).

9. Immunomodulator therapy as steroid sparing

Methotrexate: Methotrexate may have a small steroid sparing effect in adults with asthma who are dependent on oral corticosteroids. However, the overall reduction in daily steroid use is probably not large enough to reduce steroid-induced adverse effects. This small potential to reduce the impact of steroid side-effects is probably insufficient to offset the adverse effects of methotrexate (Davies, 1998)

Azathioprine : Currently there is a clear lack of evidence to support the use of azathioprine in the treatment of chronic asthma as a steroid sparing-agent. Large, long-term studies with pre-defined steroid reducing protocols are required before recommendations for clinical practice can be made (Dean, 2004)

Cyclosporine: The improvement in asthma with cyclosporin are small and of questionable clinical significance. Given the side effects of cyclosporin, the evidence available does not recommend routine use of this drug in the treatment of oral corticosteroid dependent asthma (Evans, 2001)

Chloroquine : There is insufficient evidence to support the use of chloroquine as an oral steroid-sparing agent in chronic asthma. Further trials should optimise oral steroid dosage before addition of the steroid-sparing agent (Dewey, 2003)

Troleandomycin : There is insufficient evidence to support the use of troleandomycin in the treatment of steroid dependent asthma. (Evans, 2001)

Gold: Gold has limited clinically significant benefits as steroid sparing agent & given the side effects of gold and necessity for monitoring the use of gold as a steroid sparing agent in asthma cannot be recommended. (Evans, 2001)

10. Conclusion

Inhaled Corticosteroids are the most effective first line of therapeutic intervention to control the primary immunologic mechanism of the disease and to avoid the devastating

consequences of this disease with resultant cost- effectiveness and risk benefits analysis leading to best control of asthma. As far as steroids are concerned, there is over fear of its side effects in the patients as well as physicians which has to be removed. It should be made clear that steroids are friends of asthma pts if optimally used but if overused it may turn out to be foe, hence emphasis should be given on the optimized and appropriate use of steroids based on the asthma severity, Hence physicians should try to use the both edges of this **“double edged sword”** for the benefit of patients.

In addition to pharmacological intervention, emphasis should always be given on the patient's education about asthma including its pathogenesis, medications, inhalation technique and strict environmental control on every visit of the patient. Definitely the safety issues of the use of

Steroids in asthma has to be taken in to consideration in order to address the instructions of Hippocrates, **“first do no harm”** in relation to the steroids, however steroids continue to be the most potent and the most effective controller medication for asthma, and their use in the appropriate clinical setting remains invaluable for the control & management of asthma in clinical practice.

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