Adrenal suppression: A practical manual for diagnosing and treating this under-esteemed side effect of inhaled corticosteroid in an asthmatic patient

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Abstract: Asthma remains one of the most common chronic respiratory diseases. It is estimated that approximately 300 million people of all ages and all ethnic backgrounds suffer from asthma and the burden related to this disease to governments and health care systems. The WHO (World Health Organization) has estimated that 15 million disability-adjusted life years are lost annually, and 250000 asthma deaths are reported worldwide. For the treatment of asthma, inhaled corticosteroids (ICSs) are the most effective anti-inflammatory drugs currently on the market. Inhaled corticosteroids are now widely accepted as a first-line preventive treatment in asthma increasing use is being made of high-dose inhaled corticosteroids during the step-up phase of treatment in order to optimize asthma control. Side effects of ICSs are adrenal insufficiency, a disorder known as adrenal insufficiency that occurs when the adrenal glands are unable to generate enough cortisol. It results from either deficiency or impaired action of glucocorticoids. Adrenal insufficiency (AI) is a life-threatening disorder that can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic-pituitary-adrenal (HPA) axis. Typical symptoms of AI include weakness, fatigue, anorexia, abdominal pain, weight loss and salt craving. The risk-to-benefit ratio for inhaled corticosteroids comprises their relative potencies for airway and systemic glucocorticoid activity. Fluticasone propionate (hereafter fluticasone) and budesonide are inhaled corticosteroids used for asthma. It is generally accepted that fluticasone propionate is at least twice as potent as budesonide.

KEYWORDS: Asthma, burden, Adrenal insufficiency, Inhaled corticosteroids, adrenal glands, cortisol

Introduction

Asthma is one of the most common chronic conditions worldwide [1]. It is a complicated illness that can manifest phenotypically differently in both adults and children [2]. One of the prevalent non-communicable diseases is asthma (NCDs). Approximately 339 million people worldwide are impacted by it. Asthma is among the top 20 causes of years spent with a disability and has a significant global burden of death and disability, with about 1000 people dying from it every day [3]. A chronic inflammatory disease of the airways is asthma. The chronic inflammation is linked to airway hyperresponsiveness (an exaggerated airway-narrowing response to specific triggers such as viruses, allergens, and exercise), which causes recurrent episodes of wheezing, breathlessness, chest tightness, and/or coughing that can change over time and in intensity. Symptomatic episodes are typically linked to varying and widespread airflow obstruction in the lung disease that typically resolves spontaneously or with suitable asthma medication, such as a quick-acting airway dilator [4] .For many years, there has been debate concerning the categorization and definition of asthma. Asthma, according to the Global Initiative for Asthma (GINA), is "a diverse condition, often characterised by persistent airway inflammation." In addition to fluctuating expiratory airflow restriction, it is characterised by a history of respiratory symptoms such as wheezing, chest tightness, shortness of breath, and cough that change over time and in intensity. Although not a definition in the strictest sense, this description still covers the crucial elements for therapeutic reasons [3] . According to reports, the incidence is 1-2% higher in the elderly population [1] .The prevalence of clinical asthma in Southern Asia (Bangladesh, Bhutan, India, Nepal, Seychelles and Sri Lanka) was estimated at 3.5% for a total population of 1.21 billion in the Global Initiative for Asthma (GINA) estimates [5]. Asthma affects an estimated 300 million people worldwide, and that number is expected to rise by over 100 million by 2025 [6] .

The diagnosis of asthma involves a thorough medical history, physical examination, and objective assessments of lung function in those ≥6 years of age (spirometry preferred, both before and after bronchodilator) to document variable expiratory airflow limitation and confirm the diagnosis [4]. Symptoms including sporadic dyspnoea, wheezing, coughing, and chest tightness can be used to make a clinical diagnosis of asthma [7]. The mainstay of therapy for the majority of asthma patients. The most powerful anti-inflammatory medications now used to treat asthma are inhaled corticosteroids (ICSs) [8]. The most serious adverse effect of ICS use is adrenal crisis after complete suppression of HPA-axis function. Systemic side effects, including osteoporosis, growth retardation, posterior subcapsular cataract formation, glaucoma, and skin thinning and bruising, are thought to be related to hypothalamic–pituitary–adrenal (HPA) axis suppression [9]. The most effective inhaled glucocorticosteroids on the market are budesonide and fluticasone propionate ("fluticasone") [10]. Many studies have compared the available inhaled corticosteroids, but their outcomes have been inconsistent, especially when it comes to the systemic effects of fluticasone propionate and budesonide [11]. In a prior dose-ranging study, we tried to compare the degree of adrenal suppression induced by inhaled fluticasone propionate and budesonide when given

as single doses on a microgram equivalent basis to asthmatic patients [12].

EPIDEMIOLOGY

Asthma is the 28th most common disease burden and the 16th most common cause of years lived with disability in the world, respectively [3]. The Prevalence of asthma in Asian countries varies between 5.2% in Taipei to 30% in New Zealand and in other countries, it is around 10-17 % [13]. About 6% of children and 2% of adults in India's 1.31 billion population have asthma [3].

Prevalence of Asthma in Bangalore, India –

In the hospital-based study of a general pediatric outpatient by a Pediatric Pulmonologist on international guidelines on 20,000 children under the age of 18 years in 2 decades from 1979, 1984, 1989, 1994 and 1999 in the Metropolitan cities displayed 9%, 10.5%, 18.5%, 24.5%, and 29.5%, respectively. With the city's changing demographics, the prevalence has been steadily rising. 9,1 like an increase in the number of industries, a rise in population density as a result of rural residents migrating to urban areas in pursuit of employment, and an increase in the number of cars used for commuting, all of which contribute to air pollution.

TRIGGERING FACTORS

Viral Infections: According to a clinical analysis, viral upper respiratory infections trigger asthma attacks in 40% of children. The child's parents became aware of his or her rhinitis, which was followed by a cough and fever. These kids experience chest congestion that lasts longer than 10 days and frequently includes wheezing. According to other studies, both atopic and non-atopic people experienced an incidence ranging from 29 to 54% [13].

Season: 35% of children have experienced seasonal variations in asthma attacks. Of the 35%, the incidence was 75.8% during the monsoon, 83.3% during the winter, and 2.8% during the summer.

Food: The connection between food allergies and asthma has historically been debatable, and it is particularly challenging to demonstrate in young children. When the suspected food allergen is avoided, as observed by the parents, they appear to do well. We discovered through a survey that was solely based on historical data that 19.75% of children appear to have food-related asthma, according to their parents. The most frequently accused foods are grapes (57%) followed by bananas (53%), guavas (51%), citrus fruits (28%), ice cream (21.5%), fried foods (19%), and tomatoes (12.5%), with other foods suspected to be less frequent.

Aeroallergens: Research has shown that as children get older, they become more sensitive to indoor allergens. According to studies, sensitivity increases from 1.5% at age 1 to 90% between the ages of 8 and 11. House dust mite is the main indoor allergen. Sensitivity is caused by 100 mites per gramme of dust, while wheezing is caused by 500 mites per gramme of dust. During the most humid months, Bangalore homes have 4,000–5,000 dust mites per gramme of dust. Dust mites are to blame for 50% of chronic asthma cases. Skin testing for pollen and mould sensitivity revealed only 7.5% of children older than 6 years. In Bangalore, cockroach sensitivity was noted in 25% of cases.

Irritants: Smoke, sprays, burning mosquito coils, and cooking smells are the triggering factors in 6% of children. According to a study by Cherian E, between the ages of 10 and 17 years old, 41.4% of urban children and 21.86% of rural children smoked their first cigarettes. Compared to rural agricultural labour class women, only 2% of whom smoke, 36.2% of club-going women feel that smoking is a status symbol [12].

Exercise-induced Asthma: The forced expiratory flow rate at one second decreases a few minutes after the activity has ended, demonstrating the constriction of the airways (FEV1). Since it is caused by the smooth muscle contraction of the airways, this typically peaks 5 to 10 minutes after the end of the activity and normally goes away after 20 to 30 minutes [13].

PATHOPHYSIOLOGY AND ETIOLOGY

Chronic multifactorial airway disease referred to as asthma is characterized by a complex interplay between airflow obstruction, bronchial hyper responsiveness, and chronic inflammation. The interaction of these variables affects how asthma presents clinically, how severe it is, and how well it responds to treatment [14]. T helper cell type-2 immune responses, which are typical of other atopic conditions, are linked to asthma. Both allergic and non-allergic stimuli, such as viral infections, exposure to tobacco smoke, cold air, and exercise, can act as asthma triggers and set off a chain of events that result in chronic airway inflammation. Some examples of allergic asthma triggers include house dust mites, cockroach droppings, animal dander, mould, and pollen. Increased T2 cell numbers in the airways leading to the release of distinct cytokines like interleukin (IL)-4, IL-5, IL-9, and IL-13, which in turn encourage eosinophilic inflammation and IgE production. In turn, IgE production sets off the release of inflammatory mediators like histamine and cysteinyl leukotrienes, which result in bronchospasm (contraction of the smooth muscle in the airways oedema, and increased mucous secretion, and cause the symptoms of asthma [15,16] (see figure 1).

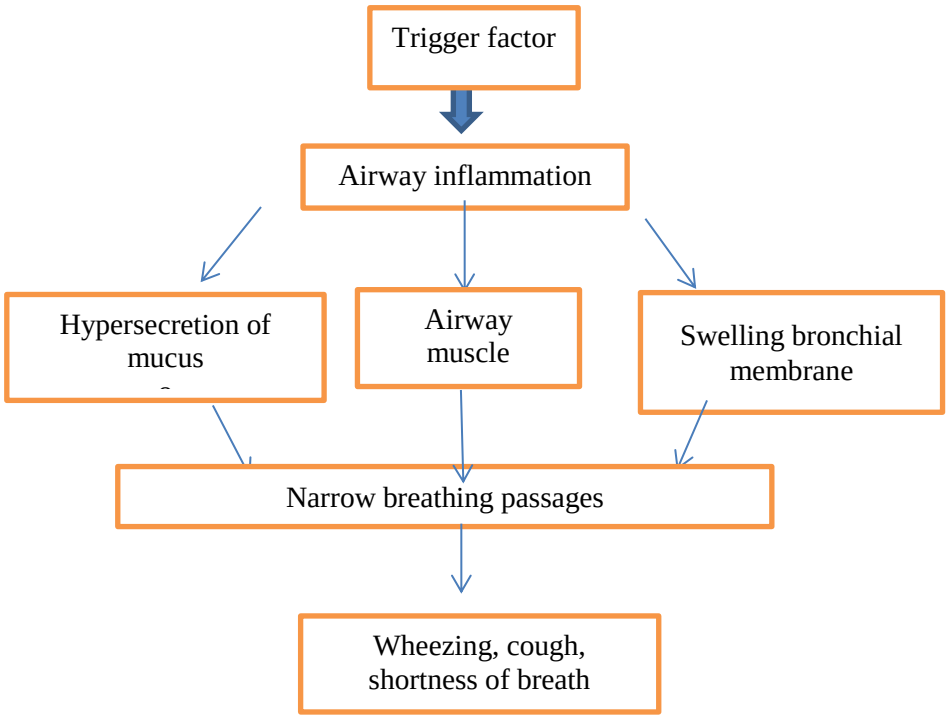

FIGURE 1: Pathophysiology and Etiology of Asthama

The mediators and cytokines released during the early phase of an immune response to an inciting trigger further propagate the inflammatory response (late-phase asthmatic response) that leads to progressive airway inflammation and bronchial hyperreactivity [16]. The frequent asthma exacerbations cause airway remodelling, which over time causes more severe airway obstruction and a decline in lung function [17]. This highlights the importance of frequent assessment of asthma control and the prevention of exacerbations [4].

Clinical Diagnosis: -

The diagnosis of asthma involves a thorough medical history, physical examination, and objective assessments of lung function in those ≥6 years of age (spirometry preferred, both before and after bronchodilator) to document variable expiratory airflow limitation and confirm the diagnosis. Bronchoprovocation challenge testing and assessing for markers of airway inflammation may also be helpful for diagnosing the disease, particularly when objective measurements of lung function are normal despite the presence of asthma symptoms. The diagnosis of asthma should be suspected in patients with recurrent cough, wheezing, chest tightness and/or shortness of breath. Symptoms that are variable, occur upon exposure to triggers such as allergens or irritants, that often worsen at night and that respond to appropriate asthma therapy are strongly suggestive of asthma [4] (see Table 1).

TABLE 1: Classification of asthma severity by clinical features before treatment [7]

Intermittent	**Mild persistent**	**Moderate persistent**	**Severe persistent**
Symptoms less than once a week Brief exacerbations Nocturnal symptoms not more than twice a month FEV1 or PEF ≥80% predicted value PEF or FEV1 variability, <20%	Symptoms more than once a week but less than once a day Exacerbations may affect activity and sleep Nocturnal symptoms more than twice a month FEV1 or PEF ≥80% Predicted value PEF or FEV1 variability, 20–30%	Symptoms daily Exacerbations may affect activity and sleep Nocturnal symptoms more than once a week Daily use of inhaled short-acting b2-agonist FEV1 or PEF 60–80% predicted value PEF or FEV1 variability >30	Symptoms daily Frequent exacerbations Frequent nocturnal asthma symptoms Limitation of physical activities FEV1 or PEF ≤60% predicted value PEF or FEV1 variability >30%

The diagnosis of asthma in children is often more difficult since episodic wheezing and cough are commonly associated with viral infections, and children can be asymptomatic with normal physical examinations between exacerbations.

Medical history

Symptoms including sporadic dyspnoea, wheezing, coughing, and chest tightness can be used to make a clinical diagnosis of asthma. sporadic symptoms following accidental allergen exposure, seasonal variations in symptoms, and a positive allergy test. Another useful diagnostic tool is a patient's family history of asthma and atopic disease. Variability; precipitation by general irritants like smoke, fumes, strong odours, or exercise; worsening at night; and response to appropriate asthma therapy are the patterns of these symptoms that strongly suggest an asthma diagnosis [7].

Physical examination

- Examine for wheezing on auscultation.
- Examine the upper respiratory tract and skin for signs of other atopic conditions [4].
- Wheezing on auscultation is the most typical aberrant physical finding, which indicates. that there is an airflow restriction. Nevertheless, even when there is a severe airflow restriction, wheezing may not be present in certain asthmatics or may only be seen when they forcefully exhale.

Measurements of lung function

Despite the fact that the presence of specific symptoms is typically enough to make an asthma diagnosis, patients with asthma frequently underestimate the severity of their symptoms, especially if they have had the disease for a long time. Additionally, medical professionals may make inaccurate assessments of symptoms like dyspnoea and wheezing. Measurements of lung function to confirm airflow limitation in patients younger than five years, particularly when it can be shown that aberrant lung function may be corrected, significantly increase diagnostic certainty.

The degree of reversibility in forced expiratory volume in one second (FEV1) that indicates a diagnosis of asthma is generally accepted as o12% and o200 mL from the pre-bronchodilator value. However, most patients with controlled asthma will not exhibit reversibility at each assessment, particularly those on treatment, and the test therefore lacks sensitivity. Repeated testing at different visits is advised. Because many lung diseases may result in reduced FEV1, a useful assessment of airflow limitation is the ratio of FEV1 to forced vital capacity (FVC). The FEV1/FVC ratio is normally .0.75–0.80, and possibly 0.90 in children. Lower values suggest airflow limitation.

Peak expiratory flow (PEF)

Readings obtained using a peak flow metre can also be a significant help in the diagnosis and management of asthma. But PEF readings are not always accurate interchangeable with other assessments of lung function, such as FEV1 in adults or children or other lung function tests, due to the variability of the values acquired from different peak flow metres and the excessively wide range of projected values. Also heavily reliant on effort, PEF readings may not be of high quality. . Therefore, measurements should always be compared with the patient's own previous best measurements using his/her own peak flow meter. The previous best measurement is usually obtained when the patient is asymptomatic and controlled. Reversibility and variability are terms used to describe changes in symptoms and variations in airflow restriction that happen naturally or in response to treatment. The term "reversibility" generally refers to either more sustained improvement over days or weeks following the introduction of an effective controller treatment, such as inhaled glucocorticoids, or rapid improvements in FEV1 (or PEF) measured within minutes after inhalation of a rapid-acting bronchodilator, such as after 200-400mg salbutamol (albuterol). Variability describes changes in symptoms and lung function over time, such as improvement or deterioration. Variability can occur over a single day (when it is referred to as diurnal variability), from day to day, from month to month, or annually. Obtaining a history of variability is crucial for making an accurate diagnosis of asthma and for determining how well the condition is being controlled [7].

Skin-allergy testing

Percutaneous (allergy skin prick) testing is advised to discover potential environmental allergic asthma triggers and is useful in determining the patient's phenotype. The allergens specific to the patient's location are often used in testing. As an alternative to skin tests, allergen-specific IgE tests that assess a patient's in vitro IgE levels for certain allergens have been proposed; however, these tests are less sensitive, more invasive (requiring venipuncture), and more expensive than skin prick tests. There is no minimum age requirement for doing skin prick tests.

MANAGEMENT

Asthma management's main objective is to establish and maintain co ntrol of the condition in order to avoid exacerbations, which are sudden, progressive worsening of asthma symptoms that frequently call for immediate medical attention and/or oral steroid therapy, as well as to lower the risk of morbidity and mortality. The therapy also aims to normalise physical activity, reduce the frequency and severity of asthma symptoms, reduce the need for pain relievers, enhance lung function, and enhance quality of life. Controllers (long-term, daily medications that control asthma primarily through anti-inflammatory effects) and relievers are two categories for the pharmacologic agents that are frequently used to treat asthma (medications used on an as-needed basis for quick relief of bronchoconstriction and symptoms) [4]. In the case of mild persistent asthma, ICS is frequently recommended as the first line therapy at low doses. Along with long-acting beta 2-agonists, they are also the preferred treatment for moderate asthma when used in moderate doses [1]. Allergen-specific immunotherapy may also be considered in most patients with allergic asthma, but must

be prescribed by physicians who are adequately trained in the treatment of allergies [18-21].

Systemic corticosteroid therapy may also be required for the management of acute asthma exacerbations. A simplified, stepwise algorithm for the treatment of asthma is provided in (see Fig. 2)[4]. The Global Initiative for Asthma (GINA) treatment recommends a stepwise method of disease management, with each step denoting a rise in the level of treatment intensity needed to achieve control [22]. The mainstay of therapy for the majority of asthma patients, For the treatment of asthma, inhaled corticosteroids (ICSs) are the most effective anti-inflammatory medications currently available. [23].

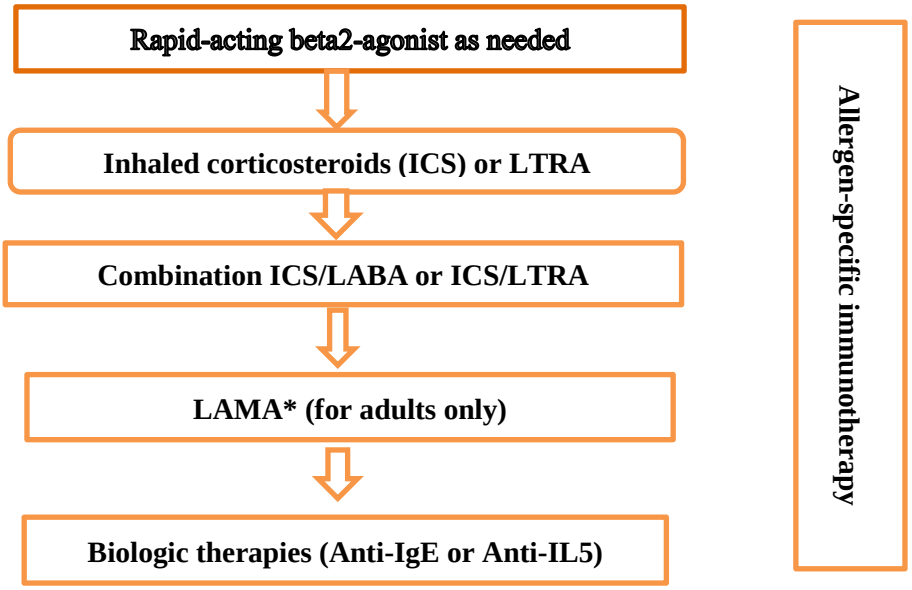

FIGURE 2: **Fig. 2** A simplifed, stepwise algorithm for the treatment of asthma. **LAMAs are not indicated in persons <18 years of age. ICS inhaled corticosteroid, LTRA leukotriene receptor antagonist, LABA long-acting beta2-agonist, IgE immunoglobulin E, IL-5 interleukin 5; LAMA long-acting muscarinic receptor antagonist.* Note: Treatments can be used individually or in any combination.

Inhaled corticosteroids

Asthma symptoms are best managed with inhaled corticosteroids (ICSs), which are frequently combined with an as-needed short-acting beta agonist for prompt symptom relief [24]. Treatment with low-dose ICS lessens asthma symptoms, improves lung function, and lowers the risk of asthma-related death [6] (see figure3).

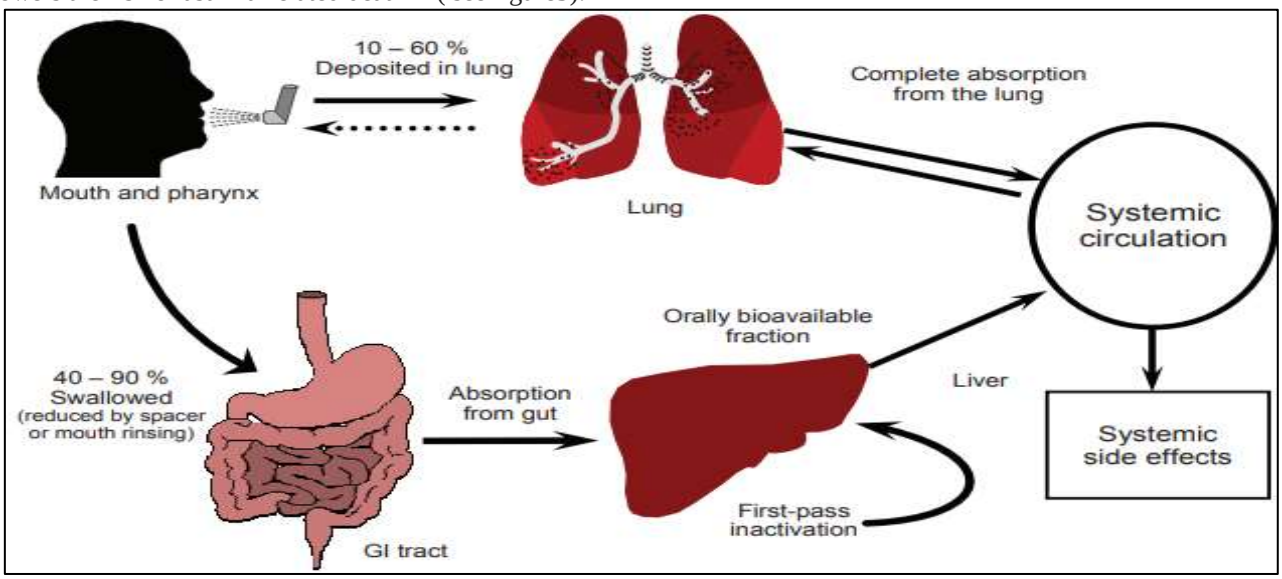

FIGURE 3 - Schematic representation of the fate of an ICS. Adapted from Ahmet A et al., 2011 [22]

Despite the fact that when used at equivalent therapeutic dosages, the different ICSs for the treatment of asthma are believed to have comparable clinical effectiveness, there are important variations in their pharmacokinetics (PK) and pharmacodynamics (PD)

that may affect their individual safety profiles. When comparing the advantages and disadvantages of each ICS medicine for a specific patient, these variations should be carefully taken into account, especially in connection to the potential for systemic adverse effects like AS. [23]. Below table provide a general summary of the PK and PD parameters that impact the safety of ICSs Characteristics, including oral bioavailability, pulmonary deposition, protein-binding, half-life, and systemic clearance.

It is useful to quickly assess the end result of an ICS in order to better comprehend the impact of PK and PD parameters on safety (see table 2).

TABLE 2: ICSs Characteristics, including oral bioavailability, pulmonary deposition, protein-binding, half-life, and systemic clearance

ICS	Oral bioavailability (%)	Lung deposition (%)	Particle size (µm)	Protein-binding (% not bound)	Half-life (h)	Systemic clearance (L/h)
Beclomethasone dipropionate	20/40*	50-60	<2.0	13	2.7*	150/120*
Budesonide	11	15-30	>2.5	12	2.0	84
Ciclesonide	<1/<1*	50	<2.0	1/1*	0.5/4.8*	152/228*
Fluticasone propionate	≤1	20	2.8	10	14.4	66

Approximately 10–60% of the given ICS is inhaled and deposited in the lungs, depending on the inhaler type. Despite the fact that ICS adverse effects are less frequent and severe than those associated with oral corticosteroids, there are still safety risks with these medications, particularly when they are administered in high dosages. One of these problems is the possibility of adrenal suppression (AS). [23]. The risk of suppressing endogenous cortisol secretion and of local side effects increases with higher doses of inhaled corticosteroids [25]. Systemic side effects of ICS are influenced by a number of variables, including the dose administered, the delivery method used, the location of delivery, and individual variations in corticosteroid response. The amount of the drug absorbed into the systemic circulation determines how an ICS will affect the body as a whole. After the portion of ICS that was deposited in the oropharynx is swallowed or after taking the medication by inhalation, absorption may take place through the digestive tract. The most severe adverse effect of ICS is dose-related suppression of the HPA axis, followed by children's growth retardation, osteoporosis, cataract, and glaucoma as well as infections and pneumonia [26].

Adrenal suppression (AS)

The most frequent cause of adrenal insufficiency is AS, which stands for insufficient or diminished cortisol production. a glucocorticoid responsible for maintaining blood pressure, blood glucose and energy levels during times of physiological stress, such as illness, surgery or injury). It can have any underlying cause (genetic, iatrogenic, acquired), and [23]. Adrenal insufficiency (AI) is a life-threatening disorder that can result from either primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic–pituitary–adrenal (HPA) axis. It results from either deficiency or impaired action of glucocorticoids [27]. When the adrenal glands are unable to produce enough cortisol, the condition is known as adrenal insufficiency (a glucocorticoid that keeps blood pressure, blood sugar, and energy levels stable while the body is under physiological stress from a sickness, operation, or injury). Any underlying factor, including genetic, iatrogenic, and acquired, may be the cause.), and it may also be linked to other adrenal hormone deficiencies, like reduced aldosterone production [23]. Typical symptoms of AI include weakness, fatigue, anorexia, abdominal pain, weight loss and salt craving [27]. There were indications of an adrenal crisis, particularly altered consciousness (seizures, coma) brought on by hypoglycaemia and evidence of HPA-axis suppression [23]. The suppression of the HPA axis caused by ICS at a given dose is its most serious side effect. ICS administration's dose, duration, and timing all affect how much suppression occurs. At doses greater than 800 ug/day/day BD equivalent, HPA suppression seems to occur in adults. Adrenal crisis following complete HPA-axis suppression is the most serious adverse effect of long-term ICS use. Adrenal crisis is uncommon, but it can be a serious concern for patients receiving unsafe doses, particularly young patients. The level of basal cortisol is frequently used as a sign of adrenal suppression. It is evident that even low-to-medium ICS doses can affect children's and adults' basal cortisol secretion, but it is unclear whether this alteration has any clinical significance [26].

Pathophysiology

The HPA axis is controlled by the circadian rhythm and functions in a negative feedback loop to control the body's secretion of cortisol. Corticotropin-releasing hormone (CRH) is released by the hypothalamus, with the morning being the time when levels are at their highest (around 6 am). After that, CRH prompts the pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal glands to release cortisol. Since cortisol inhibits the hypothalamus and pituitary gland, less CRH and ACTH are secreted, which in turn results in less cortisol being produced and secreted. This negative feedback loop enables the HPA axis to tightly self-regulate cortisol levels in the body. Exogenous glucocorticoids exert negative feedback similar to endogenous cortisol, which suppresses the production of cortisol and, as a result, results in adrenal insufficiency [28]. Since exogenous

glucocorticoids suppress cortisol production, which is crucial during times of physiological stress (such as illness or surgery), significant morbidity (adrenal crisis), and even mortality can result [23]. Corticotropin-releasing hormone (CRH) is produced by the hypothalamus and is released into the median eminence. This, in turn, stimulates the synthesis and processing of proopiomelanocortin (POMC). This results in releasing of POMC peptides including adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. ACTH binds to the melanocortin-2 receptor in the adrenal gland and stimulates the synthesis and release of cortisol into the systemic circulation. This cortisol in turn exerts a negative feedback inhibition of CRH and ACTH release. This classic example of negative feedback hormone regulation is referred to as the HPA axis [27]. Adrenal suppression is the most sensitive accessible marker currently available [29]. The disorder is characterised by an inability to produce enough cortisol [23](see figure4).

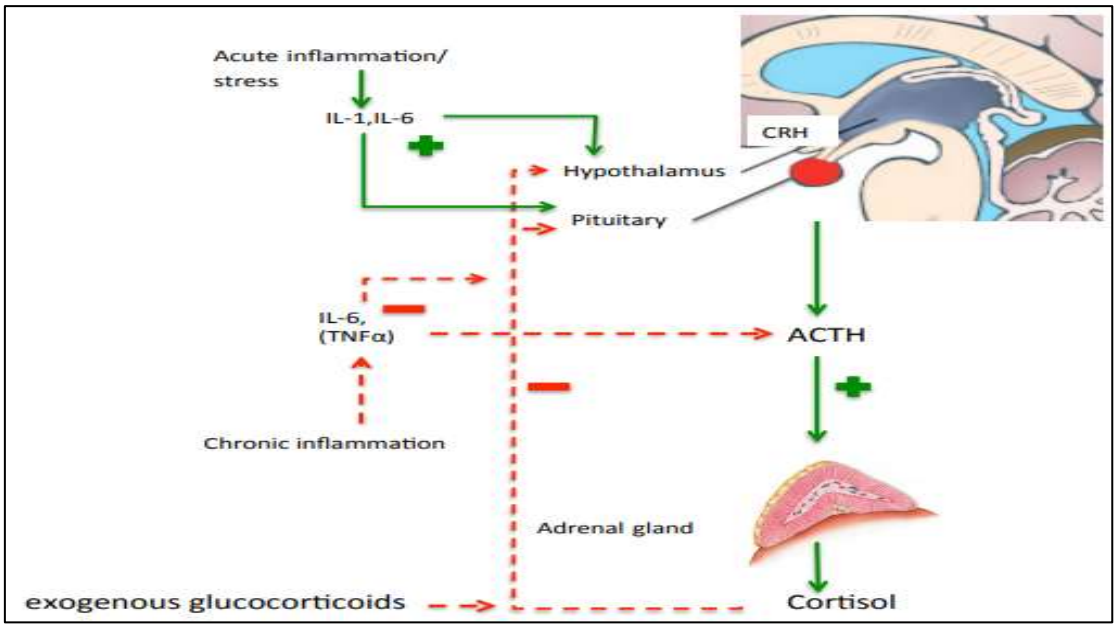

FIGURE 4 -HPA axis response to acute and chronic stress leading from inflammation. CRH-corticotrophin releasing hormone, ACT adrenocorticotrophic releasing hormone, IL-interleukin, TNF-tumour necrosis factor. Green arrows indicate activation, and red arrows indicate suppression. The HPA axis gets activated by specific cytokines released during inflammation (IL-1, IL6). IL-6 has been recognized as important in innate immune response. Acute inflammation leads to activation of the HPA axis and marked and prolonged elevation of plasma ACTH and cortisol, however chronic activation of the HPA axis leads to a blunted ACTH and cortisol response as a protective adaptation mechanism. Exogenous corticosteroids lead to suppression of the HPA axis in the same manner as cortisol that inhibits both CRH and ACTH synthesis . **Adapted from SannarangappaV et al.2014** [26]

Diagnosis

A first-morning cortisol measurement taken at 8:00 the most practical AS test available is typically more accurate and is regarded as a fair initial step for identifying suspected AS cases or for screening kids who are getting high-dose ICS therapy. If a very low cut-off value is selected (85–112 nmol/L), the specificity of this test approaches 100%; however, the sensitivity is low (60%). Adrenal function tests are frequently used to assess the possibility of systemic effects from inhaled glucocorticosteroids. Measurements of plasma cortisol concentrations over a period of 20 to 24 hours at regular intervals or measurements of free cortisol in the urine over a period of 24 hours are the two methods that are the most sensitive [30]. Despite the fact that higher cut-off values have been suggested, they have been linked to lower specificity [31]. To confirm the diagnosis if an abnormal value is found, a low-dose ACTH stimulation test should be carried out. A normal value does not exclude AS due to the inadequate accuracy of the initial morning cortisol test. If the test outcome is normal but the patient is exhibiting AS-related symptoms, a low-dose ACTH test is thus considered [23]. A random cortisol measurement is not a good indicator of AS in children because cortisol levels drop throughout the day. There are additional tests to diagnose adrenal insufficiencies, such as measuring cortisol levels in the urine or saliva, but these have not been thoroughly researched in children with AS [32-34].

Prevention

Despite the fact that Doctors and other healthcare professionals must be aware of the potential for AS in all asthma patients undergoing ICS therapy, regardless of the dose indicated, as it is the cornerstone of asthma management. Although most instances have been seen in adults using high doses of fluticasone, a few cases have been reported in patients taking modest dosages of ICS [35, 36, 37]. Healthcare experts should make the danger of AS and its symptoms known to parents of children on high ICS dosages. Parents and carers should be informed of emergency contacts in the event of serious symptoms or a suspected adrenal crisis. Poor patient monitoring and too high ICS dosages have been linked to the majority of adrenal crisis instances brought on by ICS medication [36].

Because of this, doctors should periodically review the child's ICS dose to make sure the lowest effective dose is being used to treat asthma symptoms. The overall steroid load of the patient as well as clinically significant variations across ICS drugs should be

taken into account by doctors (i.e., consider the use of all forms of glucocorticoid therapy including oral, inhaled, intranasal, intramuscular and intravenous). Consideration should be given to the use of an ICS in individuals at risk of AS that has the least adverse effects on the adrenal glands and the optimum benefit-to-side effect ratio [23].

Management

Cases with AS should, wherever feasible, be handled in conjunction with an endocrinologist. Until the first-morning cortisol reading returns to normal, daily hydrocortisone at a physiologic dose (8–10 mg/m2/day) should be taken into consideration. With an endocrinologist, the dosage and timing of daily glucocorticoid replacement should be considered. Stress steroid therapy (high dosages of hydrocortisone) in all individuals with established AS is recommended) during times of illness or surgery must be provided to simulate the protective endogenous elevations in cortisol levels that occur with physiological stress. For mild-to-moderate illness, 20-30 mg/m2 /day of hydrocortisone, it's suggested to categorize into BID or TID. In the event of an adrenal crisis, a cortisol level should be taken right away (to demonstrate suppression), the on-call endocrinologist should be contacted, and the child should receive an immediate stress dose of intravenous or intramuscular hydrocortisone (100 mg/m2), followed by 100 mg/m2 of hydrocortisone per day, divided into 3 to 4 doses over a 24-hour period [38]. Individuals who have required weeks of oral corticosteroids over a period of six months or who have been on supraphysiological dosages for more than two consecutive weeks should think about decreasing their steroid dosage to enable time for their adrenal glands to recuperate. Consideration should also be made to the use of ciclesonide in patients with established Since, as it has been demonstrated to have minimal to no suppressive effects on the HPA axis [39][40]. Information on stress steroid dosage and emergency medical contact details should be given to parents and kids who are at risk for AS. Medic-alert bracelets and/or information should be given to patients as an option. card with information about their diagnosis, current medication dosages, and stress-dosing guidelines [23].

Budesonide and fluticasone propionate

Budesonide and fluticasone propionate ("fluticasone") are the most potent inhaled glucocorticosteroids on the market [30]. Fluticasone propionate (hereafter fluticasone) and budesonide are inhaled corticosteroids used for the local treatment of inflammatory diseases in the airways, e.g., asthma and rhinitis. The desired properties of an inhaled corticosteroid for asthma include a high glucocorticoid receptor binding affinity, a high lung deposition, and a long pulmonary residence time. To minimize systemic exposure, systemic clearance should be high and volume of distribution low, leading to rapid systemic elimination. Both drugs are rapidly metabolized, with a total blood clearance approaching the hepatic blood flow [40,41]. The oral-systemic bioavailability is about 1% for fluticasone [42]and about 10% for budesonide [41]. The findings of several trials comparing the various inhaled corticosteroids have been inconsistent, especially with regard to the systemic effects of fluticasone propionate and budesonide. Whilst effects on adrenal suppression were assessed with single doses of fluticasone and budesonide, it is likely that differences between the drugs would, if anything, be more pronounced during chronic dosing because of drug accumulation at steady state with the longer elimination half-life of fluticasone. The hypothalamic-pituitary-adrenal axis is more affected by fluticasone propionate 1500 mg/day in healthy participants than in asthmatic subjects, but not by budesonide 1600 mg/day. [43]. We, therefore, reviewed the effects of two different, approximately equi-efficacious doses of both budesonide and fluticasone on adrenal function in patients with asthma[30]. In a previous dose-ranging study, we reviewed significant differences between inhaled fluticasone propionate and budesonide in the degree of adrenal suppression induced as single doses on a microgram equivalent basis in asthmatic patients [29].

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Table and figure titles and legends:

TABLE 1: CLASSIFICATION OF ASTHAMA SEVERITY BY CLINICAL FEATURE BEFORE TREATMENT

TABLE 2: ICSs CHARACTERISTICS INCLUDING ORAL BIOAVAILABILITY PULMONARY DEPOSITION PROTEIN-BINDING , HALF-LIFE, AND SYSTEMIC CLEARANCE

FIGURE 1: Pathophysiology and Etiology of Asthma

FIGURE 2: A simplified, stepwise algorithm for the treatment of asthma.

FIGURE 3: Schematic representation of the fate of an ICS

FIGURE 4: HPA axis response to acute and chronic stress leading from inflammation