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Inhaled Corticosteroids Its Evolution and Step Wise Pharmacological Treatment Strategies for All Levels of Asthma: *A Review*

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ABSTRACT

Asthma, characterized by respiratory symptoms and airflow restriction, requires a stepwise treatment approach for symptom reduction and exacerbation prevention. The Global Initiative for Asthma (GINA) aims to globally prevent, manage, raises awareness of asthma and providing yearly resources for healthcare providers. The 2023 GINA report provides practical pharmacological advice, including key changes in GINA strategy, recommended Inhaled Corticosteroid (ICS) dosages for different age groups. It explores the pathophysiology, historical evolution of asthma treatment, from smoke inhalation to modern inhalers, emphasizing cost and availability issues in low to middle-income countries like Nepal, Peru, and Uganda. Furthermore, the review emphasizes the role of pharmacogenomics in customizing asthma treatment based on individual genetic variations. Addressing potential side effects of ICS use, it proposes management strategies to minimize risks. This comprehensive approach aims to improve asthma control, reduce exacerbations, and enhance patient outcomes globally, while acknowledging the challenges faced in resource limited settings. Integration of pharmacogenomic data with clinical information enables tailored therapeutic strategies, advancing precision medicine in asthma care and improving patient quality of life.The review also highlights the issue of delayed specialist referrals for challenging asthma cases and offers revised guidelines for stepwise approaches to treatment across severity levels. It underscores the need for special considerations in low to middle-income countries due to limited access to inhaled medications. Overall, the review advocates a holistic approach to asthma management, combining pharmacology with genetic insights and improved healthcare delivery, to address the complexities of asthma care worldwide.

Keywords: Global Initiative for Asthma (GINA), Inhaled corticosteroids (ICS), Anti-inflammatory, Asthma, COPD.

INTRODUCTION

Asthma, a type of obstructive airway disease, was first described in ancient Greek as "noisy breathing." Asthma is a long-term respiratory condition that impacts individuals globally. As of May 4th 2023, the most recent report from the World Health Organization (WHO) states that around 262 million individuals globally suffered from asthma in 2019, resulting in 455,000 deaths. This is because of the fundamental pathophysiology involving persistent inflammation in the airways [1]. When not effectively controlled, this inflammation results in a progressive reduction in lung function over time. Repeated episodes of airway inflammation give rise to a range of symptoms including coughing, tightness in the chest, wheezing and tightness in the chest. These symptoms change in both duration and severity, and are accompanied by varying degrees of expiratory airflow restriction, leading to considerable rates of death and illness [2].

The Global Initiative for Asthma (GINA) was established in 1993 with the collaboration of WHO and the US National Heart Lung and Blood Institute to improve worldwide understanding, prevention, and treatment of asthma [3]. The GINA guidelines serve as a comprehensive, evidence-based strategy for asthma management and prevention, annually updated to reflect the latest best practices in the field. These guidelines aim to provide clinicians with practical guidance on confirming asthma diagnosis, personalized

asthma management, and regular assessment of modifiable risk factors to optimize asthma outcomes. While GINA guidelines offer a global perspective, it is crucial to adapt these recommendations to suit local healthcare systems, considering factors such as healthcare infrastructure, resource availability, cultural considerations, and socioeconomic factors that may influence their implementation in diverse regions. By aligning with GINA guidelines, healthcare providers can benefit from improved asthma outcomes, standardized care practices, and enhanced collaboration among healthcare professionals. However, challenges related to accessibility, affordability, acceptability, and sustainability of asthma care interventions must be addressed when implementing GINA guidelines in different healthcare settings [3-4]

Key changes in the GINA strategy report relevant to clinical practice include: 1) Expanded indications for starting regular controller treatment: The GINA report now includes a new table with evidence-based recommendations for initiating controller treatment, such as earlier initiation of low-dose inhaled corticosteroids for patients with symptoms twice or more a month and/or risk factors for exacerbations. 2) Tailoring asthma treatment for individual patients: The GINA report describes a framework for personalized asthma management, considering factors such as symptom control, risk factors, lung function, and patient preference. 3) Assessment of asthma control: The GINA report emphasizes the importance of assessing asthma control from two domains: symptom control and risk factors, and no longer includes lung function as a measure of symptom control. 4) Asthma severity: The report clarifies that asthma severity is a retrospective label, assessed from treatment needed to control asthma. 5) Practical tools and clinical algorithms: The GINA report provides practical tools and clinical algorithms to help clinicians distinguish between uncontrolled and severe refractory asthma. These updates aim to improve the implementation of evidence-based recommendations in clinical practice, ultimately leading to better asthma control and reduced risk of exacerbations [2,4-6].

A systematic search strategy was employed to gather relevant research on asthma management. Electronic databases like PubMed, Google Scholar and MEDLINE were searched for publications addressing asthma management. Keywords and Medical Subject Headings terms related to the topic were used. Studies were selected based on pre-defined criteria (e.g., study design, population). Software tools might have been used for initial screening and duplicate removal. Data extraction focused on key findings and details from the GINA 2023 report. A narrative synthesis approach will likely be used to summarize and interpret the findings. This review article explores current asthma management, tracing its evolution from historical practices to modern inhalers. It examines the 2023 GINA report's emphasis on personalized medicine, including tailoring treatment based on symptoms, risk factors, and pharmacogenomics. By integrating pharmacology, these advancements, and improved healthcare delivery, the review highlights the potential for better global asthma control and patient outcomes, while acknowledging challenges in resource-limited settings.

Brief History of Asthma Treatment

Asthma is derived from the Greek word meaning "short ness of breath," which indicated that every patient suffering dyspnoea had asthma. The historical progression of asthma management has evolved significantly over time, from ancient remedies like smoke inhalation to the development of modern inhalers and advanced therapies. In ancient times, various treatments were attempted, such as drinking wine or inhaling smoke from burning jimson weed [9]. In the latter half of the 1800s, Henry Hyde Salter's treatise "On Asthma and its Treatment" was published, which helped to refine the word. In this research, Salter provided a definition for asthma that captures his idea of the disease: "Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration during attacks." The disease causes the airways to narrow as a result of smooth muscle tension [7]. Approximately thirty years prior to Paul Ehrlich established aniline stains for mast cells and eosinophils, remarkably depicted

airway conditions in asthma and bronchitis. He also mentioned black coffee, containing theophylline derivatives, as a treatment for asthma symptoms. [7- 8] The doctor needed to first rule out infectious illnesses or internal organ conditions like mitral stenosis, both common during that era. Once confirming a respiratory disorder, treatment options were unfortunately quite limited at the time. Inhaling smoke from burning jimson weed was probably the most straightforward remedy, as it was commonly used at the time. This drug was the precursor of the antimuscarinic drugs that are today prescribed, such as ipratropium and tiotropium, and it possessed anticholinergic properties [9]. There have been a number of different treatments, such as breathing in hydrocyanic acid fumes or using a bellows inflating the lungs. Fortunately, these kinds of treatments along with many more that were not profitable and likely caused harm, are no longer being utilized [10].

Sir William Osler in 19th century described asthma as a disease characterized by bronchial spasms and identified triggers like climate, emotion, and diet.As per Osler's 1914 eighth edition of Principles and Practise of Medicine, hypodermic injections of alkaloids are an effective treatment for bronchial asthma. He goes on to say that antispasmodics with sedative properties, like belladonna, “may be administered in the form of cigarettes” [7]. In 1914, common asthma treatments like lozenges and cigarettes contained plants from the potato family, with effectiveness varying among patients. Anticholinergics, either injected or inhaled, were considered mainstays for asthma treatment. Osler noted individual responses to treatments, reflecting modern understanding of genetic variances contributing to adverse reactions.

Atropine, belladonna, and stramonium leaf smoke are also suggested by Francis Rackemann in Cecil's A Textbook of Drugs, published in 1927. This suggestion persists in the seventh edition of Cecil's A Textbook of Drugs, released in 1947 [10], wherein Rackemann continues to support the use of alkaloids of the belladonna type in powder form for respiratory conditions or in cigarettes for asthma. But as J.B.L. Howell pointed out when he excluded belladonna alkaloids from the regular edition of the textbook in 1975, they were no longer regarded as a major part of treating asthma [10]. Between 1928 and 2012, our understanding of respiratory diseases underwent three significant transformations. First, spirometry, developed in the preceding decade, was refined by incorporating time and volume data, enabling the use of forced exhalation measurements in diagnosing and treating respiratory diseases from the late 1940s to early 1950s. Fourteen different lung-function tests were developed, shedding light on the connections between symptoms and clinical physiology. The relation between clinical physiology and symptoms were clarified by the development of fourteen different lung-function tests. Second, glucocorticoids were recognized as effective treatments for respiratory illnesses. They were first used to improve patient care systemically in the early 1950s. Later, inhaled versions of them became available, further improving patient care even now. Third, our comprehension of the immunobiology of respiratory diseases improved. It was revealed that the primary mechanism involved immediate hypersensitivity reactions. Despite advancements in understanding respiratory disease cell biology, these discoveries have not yet resulted in new treatments, although some new therapies have been developed based on our improved understanding of immediate hypersensitivity reactions, including the use of anti-IgE antibodies and leukotriene modifiers [11-12].

Recent advancements focus on identifying genetic factors contributing to asthma and developing targeted therapies based on improved understanding of immune reactions. This historical context underscores the significant advancements in managing asthma, transitioning from symptomatic relief to targeted inflammation control and personalized treatment approaches [8,13].

Some of the most significant advancements in asthma treatment in the past decade include the introduction of biologics for severe asthma management. Biologics, such as omalizumab, have revolutionized severe asthma treatment by targeting specific immune system components like IgE to reduce airway inflammation. Additionally,

triple-drug therapy, combining corticosteroids and long-acting beta-agonists with a third medication, has shown promising results in managing severe asthma. The use of connected technologies and inhaler-based medicines has improved patient access and outcomes, while advancements in personalized treatment approaches and the development of new drugs have enhanced the overall landscape of asthma management. These innovations have led to real and measurable improvements in patient care, marking an exciting era in asthma research and treatment [14,15].

Levels of asthma

Asthma severity is categorized into four levels depending on its intensity. The severity of asthma levels according to GINA classification by clinical features prior to treatment is displayed in the following table. (See Table 1) [16-18].

Table (1): Severity of asthma levels according to GINA classification by clinical features prior to treatment.

Asthma levels based on severity	Day Symptoms	Symptoms at night	FEV1 or PEF	PEF variability
Intermittent	< 2 Time a week, and normal PEF in between attacks	<2 times a month	80 %	<20%
Mild Persistent	> 3 time a week but < 1 time a day	1 time per week	≥ 80%	20-30%
Moderate Persistent	Daily attacks impact on activity.	>1 time a week	60%-80%	> 30%
Severe Persistent	Ongoing restricted physical movement	Frequent	≤ 60%	> 30%

FEV1: forced expiratory volume in one second, PEF: peak expiratory flow rate.

Having asthma requires understanding both your airway condition and the typical symptoms associated with the condition. Familiarity with these symptoms is crucial for identifying triggers, determining when immediate relief medications are necessary, and recognizing situations that require urgent medical attention.

Asthma leads to three specific changes in your airways (see figure 1):

1. Inflammation of the respiratory tract.
2. A build-up of mucus obstructs the airways.
3. The muscles surrounding the airways contract and tighten.

The inflammation, muscle constriction and congestion cause your airways to become narrower. This obstruction makes it challenging for air to flow freely through your respiratory passages, making breathing more difficult [17]. This results in the symptoms of asthma, also known as asthma episode or attack, which can occur unexpectedly. While more severe asthma symptoms or attack may start hours or days later, milder symptoms may just last a few minutes. Breathing feels tough and uncomfortable, like trying to breathe through a straw filled with cotton [18].

Pathophysiology of asthma

Asthma is a long-term lung problem where the airways get swollen, making them overly sensitive and causing difficulty breathing. This condition involves a mix of chronic inflammation, increased sensitivity of the air passages, and reduced airflow. How these factors work together affects how severe the asthma symptoms are and how well treatment works (See figure 1 pathophysiology of asthma) [19].

Airway Inflammation

The acute stage of inflammation

In individuals prone to allergies, when they breathe in allergens, such as pollen or dust, these substances get trapped in the mucus lining of their airways. Antigen-presenting cells, particularly dendritic cells, then pick up these allergens. Following this, dendritic cells present the allergens to naive CD4+ T cells. The way these cells interact determines whether the naive CD4+ T cells will transform into T-helper type 1 (Th1) or T-helper type 2 (Th2) cells. In people with

allergic asthma, there tends to be a prevalent Th2 response, which promotes the development of allergic inflammation in the airways [14]. The presence of high-affinity IgE receptors on mast cells triggers a process known as degranulation, leading to the release of pre-synthesized mediators. This release subsequently induces bronchoconstriction, airway swelling, and damage to nearby tissues [19].

The late stage of inflammation.

During the later stage of inflammation, chemicals released by mast cells attract eosinophils, basophils, neutrophils, and lymphocytes, all playing a role in prolonging the inflammatory process. Eosinophils, in particular, emerge as the key and abundant inflammatory cells at this stage. Th2 cells produce IL-5, which amplifies eosinophil growth, development, and movement, leading to the release of harmful granular proteins, alongside additional cytokines and chemokines. Eosinophil activity results in tissue damage, excessive mucus production, heightened permeability of blood vessels, muscle tightening, and a persistent inflammatory response. This sets the stage for the recruitment of other cell types to the inflammation site, perpetuating the reaction [20].

Airway hyperresponsiveness

Airway hyperresponsiveness refers to an exaggerated narrowing of the airways in response to various triggers. Factors like inflammation, nervous system dysfunction, and structural alterations contribute to this hyperresponsiveness, with inflammation being a significant determinant of its severity. It's widely recognized that therapy involving ICS effectively reduces airway hyperresponsiveness in individuals with asthma [19].

Bronchoconstriction

The narrowing of airways, stands as the primary physiological process driving clinical symptoms in asthma. Allergen-induced bronchoconstriction arises from IgE-triggered mast cell degranulation, releasing mediators like histamine, tryptase, leukotrienes, and prostaglandins. In some patients, aspirin and similar nonsteroidal anti-inflammatory drugs prompt mediator release and bronchoconstriction through a non-IgE-dependent mechanism. Additionally, stimuli such as exercise, cold air, and irritants can induce acute airflow obstruction in certain individuals [18].

Airway Remodelling

Chronic airway inflammation in asthma can lead to airway remodelling, characterized by permanent changes such as thickening of the basement membrane, fibrosis, smooth muscle enlargement, blood vessel dilation, and increased mucous gland activity. This process, driven by complex interactions among various cell types, results in irreversible airflow limitation, persistent disease, progressive loss of lung function, and limited response to therapy. ICS target this inflammation by binding to glucocorticoid receptors, though corticosteroid resistance may occur in smoking asthmatics and severe cases due to decreased histone deacetylase-2 activity, impairing the ability to deactivate inflammatory genes effectively [19- 22].

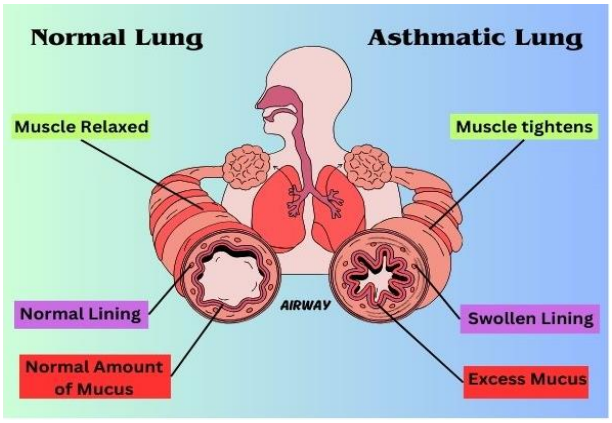

Figure (1): Pathophysiology of asthma.

Inhaled corticosteroids

In asthma treatment, inhaled corticosteroids (ICS), also called glucocortico steroids, glucocorticoids, and steroids, are highly effective at calming inflammation in the airways, even in small doses [23].

ICS are the primary treatment for asthma management and exacerbations. They work by reducing inflammation in the airways, which helps prevent asthma symptoms and flare-ups. ICS are anti-inflammatory drugs that also modulate the immune response in the airways, leading to better asthma control and fewer symptoms. They are typically used in combination with other asthma medications, such as long-acting beta-agonists or leukotriene receptor antagonists, to provide comprehensive asthma management [24].

In the past decade, significant advancements in asthma treatment have been made, particularly in the use of ICS. The 2023 GINA strategy report recommends that all adults, adolescents, and most children with asthma should receive ICS-containing therapy to reduce the risk of asthma exacerbations and improve asthma control. The report also emphasizes the importance of personalized treatment approaches, considering factors such as age, severity of asthma, and treatment response [25]. For adults and adolescents with mild asthma, the preferred regimen is maintenance-and-reliever therapy (MART) with ICS-formoterol, while for patients with moderate-to-severe asthma, the recommended regimen is combination ICS-formoterol. The report also highlights the need for ongoing medication decisions based on the patient's needs within a track, using the same reliever. Additionally, the report stresses the importance of addressing modifiable risk factors and comorbidities, checking and correcting adherence and inhaler technique, and considering the use of biologic therapy based on the patient's inflammatory phenotype [24-26].

Mechanism of action of Inhaled Corticosteroid

ICS molecules attach to glucocorticoid receptors (GR) in the cytoplasm after diffusing through the cell membranes of respiratory epithelial cells and other cells in the airway [19]. The glucocorticoid-response elements (GRE) in the promoter region of steroid-sensitive genes, which may produce anti-inflammatory protein molecules, are bound by the steroid-receptor complex after it moves into the nucleus. Overall, there is an increase in the transcription of anti-inflammatory genes and a suppression of activated inflammatory genes. ICS lessen airway hyperresponsiveness and regulate asthma symptoms by suppressing airway inflammation. Many of the side effects of corticosteroids are caused by suppression of gene transcription. For example, osteocalcin is expressed in a manner that is inhibited by corticosteroids and plays a role in bone synthesis. In asthma treatment, it's thought that inhaled corticosteroids (ICS) increase the number of β2 receptors on cell membranes, while β2-agonists may indirectly enhance the anti-inflammatory effects of ICS [19, 26-27].

In smoking asthmatics and severe asthma patients, corticosteroid effectiveness is relatively low, unlike those with chronic obstructive pulmonary disease (COPD), where corticosteroid response is generally poor. This is due to reduced activity and expression of histone deacetylase-2 (HDAC2) in these patient groups, which prevents corticosteroids from deactivating inflammatory genes [26]. Normally, activated glucocorticoid receptors (GR) recruit HDAC2, which reduces inflammation by modifying gene activity. However, oxidative stress from cigarette smoke and intense inflammation in severe asthma and COPD diminish HDAC2 activity, reducing the anti-inflammatory impact of corticosteroids [26, 28].

Anti-inflammatory effect of corticosteroid in asthma

It reduces the inflammation by decreasing the eosinophil number and increasing the apoptosis of eosinophils [29]. It decreases the cytokine release from T lymphocytes, decreases the activity of mast cell numbers, and decreases the cytokine release from macrophages; it also decreases the dendritic cell numbers, which contain antigen. It has structural cells in the respiratory track, it decreases cytokine and other inflammatory mediators release from epithelial cells,

decreases plasma leak from the endothelial cells, decreases the cytokine and increases the beta 2 receptor numbers so bronco relaxation can occur, and it also decreases the mucus secretion from mucus glands [30].

The use of corticosteroids hinders respiratory tolerance

The ability of the respiratory system to tolerate innocuous antigens entering the lungs through inspired air is a very effective mechanism for reducing inflammation in the airways and limiting the immune system responses. In a study led by Philippe Stock and colleagues, it was observed that the use of dexamethasone hindered the enhancement of respiratory tolerance. This resulted in increased proliferation and cytokine secretion by antigen-specific T cells, along with airway hyperreactivity. Additionally, dexamethasone suppressed Interleukin (IL)-10 synthesis in dendritic cells (DCs) within the mice with tolerated lungs, diminishing their ability to transmit tolerance and promote the formation of antigen-specific regulatory T (TReg) cells. As a result, while corticosteroids may alleviate acute allergic inflammation, they might additionally obstruct the immune system's reaction known as respiratory tolerance from developing, which is essential for controlling T helper 2 (Th2) cell to allergic respiratory inflammation [31-33].

Beta-2 adrenergic agonists

Beta-2 adrenergic agonists, such as salbutamol and formoterol, are widely used in asthma treatment due to their bronchodilatory effects. These agonists primarily act on airway smooth muscles by binding to beta-2 receptors, triggering a cascade of events leading to smooth muscle relaxation [34-35].

Mechanism of action of Beta-2 adrenergic agonists

Beta-2 adrenergic agonists work by relaxing airway muscles through the stimulation of specific receptors, leading to bronchodilation. The activation of beta-2 adrenergic receptors induces bronchodilation and relaxation of airway smooth muscles, crucial in enhancing airflow in individuals with asthma. By binding to these receptors, beta-agonists trigger a cascade of events that lead to the relaxation of the smooth muscle cells lining the airways. This process involves an adrenergic receptors are linked to a stimulating G protein that triggers adenylyl cyclase (AC). This enzyme generates cAMP as a second messenger. In the lungs, cyclic adenosine monophosphate (cAMP) reduces calcium levels in cells and activates protein kinase A (PKA). These changes deactivate myosin light-chain kinase (MLCK) and activate myosin light-chain phosphatase (MLCP). On the other hand, muscarinic antagonists contribute to bronchodilation by blocking acetylcholine (Ach), a substance that typically triggers the contraction of airway smooth muscles. By inhibiting acetylcholine's (Ach) action at receptor sites, muscarinic antagonists indirectly prevent the tightening of airway muscles, promoting smooth muscle relaxation. Moreover, beta-agonists can also influence membrane K+ channels, further promoting muscle relaxation without a significant rise in cAMP levels. These mechanisms collectively contribute to the improved airflow and relief of bronchoconstriction experienced by individuals with asthma. The Figure 2. Explains how bronchodilators work to relax smooth muscles in the airways. Beta-2 adrenergic receptor agonists not only directly relax muscles but can also reduce signals from the parasympathetic ganglia by activating specific receptors. This double action helps in overall muscle relaxation and bronchodilation, making breathing smoother [35-37]

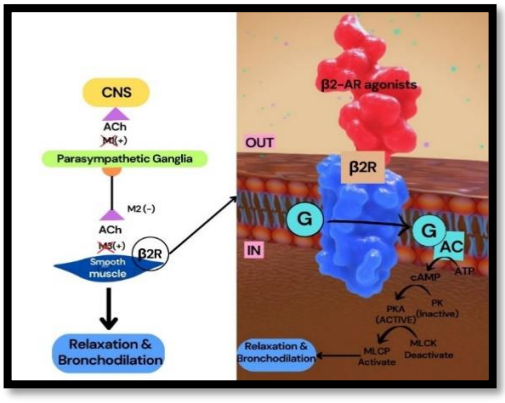

Figure (2): Bronchodilators work to relax smooth muscles in the airways.

Step wise Pharmacological approaches to treating asthma at every level of severity

GINA 2023 updated guidelines suggested the following steps focusing on risk reduction.

According to GINA, the main objectives of asthma treatment are to achieve the best possible asthma control and lowering the risk of flare-ups, mortality, reduction in lung functionality and negative side effects of medication [4].

Step 1: For adults and adolescents, Step 1 involves the use of low dose ICS-formoterol necessary for relief of symptoms (an anti-inflammatory medication), and patients with mild asthma, who have symptoms that occur less than twice a week and less than two night-time awakenings per month, are prescribed to use short-acting beta-2 adrenergic agonists (SABA) on an intermittent basis [4,40].

Step 2: In step 2, the typical dosage of budesonide-formoterol as needed for mild asthma is one inhalation of 200/6 mcg (or 160/4.5 mcg delivered dose), taken when symptoms are relieved. If as needed ICS-formoterol is unavailable and the patient is unlikely to take regular ICS, another option is to use SABA inhalers in combination or separate ICS inhalers [4,41].

Step 3: In Step 3 of asthma management, Maintenance and Reliever Therapy (MART) with low-dose budesonide-formoterol or beclomethasone-formoterol is recommended. The typical prescribed doses are 200/6 mcg for budesonide-formoterol and 100/6 mcg for beclomethasone-formoterol, taken as one inhalation twice daily for maintenance and as needed for symptom relief [4,42].

Step 4: In Step 4 of the GINA report, the MART regimen can be implemented by increasing the twice-daily maintenance dose to two inhalations of moderate-dose beclomethasone-formoterol or budesonide-formoterol. The reliever dose remains at 1 inhalation of low-dose ICS-formoterol as needed, with standard doses of 100/6 mcg for beclomethasone-formoterol and 200/6 mcg for budesonide-formoterol, both taken as two inhalations twice a day for maintenance and one inhalation when required for symptom relief [4,41].

Step 5: Add on therapy: Add-on therapy for severe asthma may include low-dose azithromycin, long-acting muscarinic antagonists (LAMA), high-dose ICS-LABA combinations, and biologic agents tailored to the inflammatory phenotype and clinical features. Oral corticosteroids should be a last resort due to potential long-term side effects, with bisphosphonates recommended to prevent osteoporosis [4,43]. Omalizumab, an anti-IgE monoclonal antibody, can benefit individuals with atopic conditions by reducing steroid dependency and improving symptom management [44].

Step-down therapy

Achieving and maintaining optimal asthma control for 2-3 months, along with reaching a stable level of lung function, often allows for successful reduction of treatment without compromising asthma management [4, 45]. To determine the least amount of treatment necessary for the patient, aiming to uphold effective control over symptoms and prevent exacerbations, while minimizing both the financial expenses and the potential side effects associated with the treatment [46]. To motivate the patient to keep receiving maintenance care, because they are worried about the expenses or risk associated with daily treatment, patients frequently experiment with intermittent treatment, which exposes them to the risks associated with SABA alone [45]. There is an alternative for patients whose asthma is well controlled on maintenance low-dose ICS with as-needed SABA, discontinuing maintenance ICS and switching to as-needed low-dose ICS-formoterol [46-47].

Before stepping down

Each patient's step-down procedure for asthma treatment is vary and based on their preferences, risk factors, and present therapy [48]. Limited data are available regarding the most effective timing, order, and extent of reducing asthma treatment. Some factors that make it more likely for someone to have problems after reducing treatment include having had asthma attacks or emergency visits for asthma in the past year [49-50] and having a low baseline Forced Expiratory Volume 1 (FEV1) [51]. Other signs of losing control when reducing medication include airway hyper responsiveness and sputum eosinophilia [50]. Stepping down a regimen of treatment should always be viewed as a therapeutic trial, with response to treatment measured in terms of frequency of flare-ups as well as control of

symptoms. A handwritten asthma remedy strategy and recommendations on when to start their prior therapy should be given to the patient before they step down, in case their symptoms get worse [4, 52].

How to step down asthma treatment

Determinations regarding the adjustment of treatment should be personalized for each patient. In a study involving individuals with adequately controlled asthma using a moderate dose of inhaled corticosteroid (ICS) and LABA. Cutting down on the ICS dosage and stopping the LABA had similar impacts on a combined therapy failure outcome. Nevertheless, ceasing the LABA was associated with worsening lung function along with increased hospital stays, and lowering the ICS dose proved less effective than maintaining a consistent dosage of ICS-LABA [51]. Stepping down from daily low-dose inhaled corticosteroids (ICS) along with beta-2 agonists (SABA) to only using ICS-formoterol as needed offers similar or even better protection against severe episodes of asthma and the requirement for emergency medical treatment. When compared to the daily use of low-dose ICS plus as needed SABA, this approach significantly reduces the average daily ICS dose while maintaining similar control of symptoms and function of the lungs [4, 52].

Recommended dosage for ICS in adults, adolescents and children with asthma according to GINA guidelines 2023

Inhaled corticosteroid dose range for adults and adolescents (12 year and over)

According to the GINA guidelines 2023, the recommended dosages for inhaled corticosteroids (ICS) in adults with asthma vary based on the severity of asthma and the specific treatment approach [4,23]. For adults with mild asthma, maintenance-and-reliever therapy (MART) with low-dose ICS/formoterol (160/4.5 µg for BUD/FOR or 100/6 µg) is recommended. It is crucial not to exceed the maximum daily dose of formoterol when using the MART approach. For patients with moderate-to-severe asthma, the preferred regimen is combination ICS/formoterol [2,25]. The maximum recommended daily dose of formoterol for patients 12 years and older is a total of 54 µg, including doses used for maintenance [4]. These dosages aim to optimize asthma control and reduce the risk of exacerbations while considering individual patient needs and treatment responses. Inhaled corticosteroid dose range for adults and adolescents (12 year and over) [4, 38-39].

Table (2): Inhaled corticosteroid dose range for adults and adolescents (12 year and over).

Inhaled Corticosteroid (ICS)	Total metered dose/ day (micrograms)		
	Low	Moderate	High
Budesonide	200-400	>400-800	>800
Ciclesonide	80-160	>160-320	>320
Mometasone furoate		200-400	>400
Fluticasone furoate	100		200
Fluticasone propionate	100-250	>250-500	>500
Beclomethasone dipropionate	100-200	> 200-400	>400

Inhaled corticosteroid dose range for children (6-11 years)

In children aged 6 to 11 years with asthma, the recommended dosages of inhaled corticosteroids (ICS) vary based on severity. The dosages range from 80 to 320 micrograms per day, depending on whether it is a low, moderate, or high dose, administered as a single dose or in divided doses [4]. For children under 5 years old, the maximum recommended dose is 400 mcg/day, and for those aged 5 to under 12 years, it is 800 mcg/day; doses exceeding 800 mcg/day are not licensed due to potential adverse effects [2]. It is crucial to avoid using short-acting beta-2 agonists (SABA) alone in children over 5 years old and prioritize ICS-containing therapy to reduce the risk of severe exacerbations. Inhaled corticosteroid dose range for children (6-11 years) See Table 3 [4].

Table (3): Inhaled corticosteroid dose range for children (6-11 years).

Inhaled Corticosteroid (ICS)	Total metered dose/ day (micrograms)		
	Low	**Moderate**	**High**
Budesonide	100-200	>200-400	>400
Ciclesonide	80	>80-160	>160
Mometasone furoate		100	200
Fluticasone furoate	50		n.a.
Fluticasone propionate	50-100	>100-200	>200
Beclomethasone dipropionate	50-100	>100-200	>200

Consideration of pharmacogenomics used in asthma

The fields of genomics and pharmacogenomics offer the potential to enhance asthma control and reduce future risks associated with the condition [53]. Pharmacogenomics plays a crucial role in customizing asthma treatment by identifying genetic variations that influence responses to medications, optimizing medication choice, and dosages [53-54]. This personalized approach, combined with ongoing research in pharmacogenomics, aims to improve treatment outcomes while minimizing side effects [55]. Factors like age, comorbidities, environmental exposures, and other medications also impact asthma therapy complexity. Integrating pharmacogenomic data with clinical information provides a comprehensive view of individual patient profiles, enabling tailored therapeutic strategies and advancing precision medicine in asthma care to enhance patient outcomes and quality of life [53-54].

Cost-effectiveness in asthma treatments

Determining the most cost-effective asthma treatment involves a nuanced approach that considers short-term costs like medication acquisition and delivery devices, as well as long-term costs and benefits such as hospitalizations, work productivity loss, and quality of life improvements. Inhaled corticosteroids (ICS) are fundamental for long-term control due to reduced exacerbations, with their initial cost balanced by long-term benefits. Long-acting beta agonists (LABA) as add-on therapy and combination therapies like ICS and LABA in a single inhaler vary in cost-effectiveness based on asthma severity and adherence [56]. For severe cases, biological therapies such as omalizumab can be highly effective despite their significant initial cost, showing potential cost-effectiveness in specific patient groups with reduced hospitalizations and improved quality of life [57]. Individualized assessment by healthcare professionals is essential to consider both clinical effectiveness and cost-effectiveness in personalized asthma treatment plans, factoring in variables like asthma severity, medication response, and insurance coverage [58].

Global availability of asthma medications

Globally, the prevalence of chronic respiratory illnesses is rising, with low- and middle-income countries (LMICs) experiencing the highest rates of disease-related mortality and morbidity [59]. An estimated 174 million people worldwide suffer from obstructive respiratory diseases like asthma, and 358 million from COPD [60]. Several studies have looked at the cost and accessibility of necessary drugs for the treatment of asthma and COPD in low-income countries settings, but these studies have typically only looked at a smaller number of pharmacies in rural as well as urban areas. With an aim of 80% availability of affordable medical supplies as well as vital medications to treat noncommunicable conditions, the WHO states that access to essential medications for noncommunicable conditions has been deemed a health care priority. The WHO lists the following drugs as essential necessities for a basic health system: beclomethasone, budesonide, budesonide/formoterol, ipratropiom bromide and salbutamol aerosolized therapy, and epinephrine injection [61]. In a study, Trishul Siddharthan et. al, and others they surveyed 63 pharmacies in Nepal (95.2% private), 104 pharmacies in Peru (94.2% private) and 53 pharmacies in Uganda (98.1% private). During the period spanning 2017 to 2019,

researchers engaged with both private and public pharmacies situated within the specified regions of the global Excellence in COPD outcomes study sites, which included Bhaktapur, Nepal, Lima, Peru, Nakaseke and Uganda. The purpose was to evaluate the pricing and availability of medications for the management of asthma and COPD [60].

Availability of short-acting muscarinic and beta antagonists

Among the three places (93.7% Nepal, 86.5% Peru, and 79.2% Uganda), salbutamol (WHO-EML) monotherapy in any composition was the most widely accessible respiratory drug. All three of the research places combined had 65.5% of pharmacies selling salbutamol monotherapy inhalers (87.3% in Nepal, 69.2% in Peru, and 32.1% in Uganda). Salbutamol monotherapy inhalers were not significantly more readily available in private pharmacies in Nepal (88.3%) than in public pharmacies (66.6%) ($p = 0.22$). But at 34.1% pharmacies in all three study sites 82.5% in Nepal and 22.1% in Peru ipratropium bromide inhalers were less common than salbutamol ($p < 0.05$). In Nepal, there was uniform availability of ipratropium bromide inhalers across all public pharmacies, with no discernible differences noted [60].

Availability of oral corticosteroids

Oral corticosteroids (OCS) are stocked by the majority of pharmacies across all three locations, with availability rates of 71.4% in Nepal, 87.5% in Peru, and 100% in Uganda. Generic forms of OCS are also widely accessible. Prednisone was found to be widely available in most pharmacies in Uganda (88.7%), while dexamethasone was prevalent in the majority (98.1%). In Peru, prednisone and dexamethasone were also readily accessible, with availability rates of 86.5% and 78.9%, respectively. OCS was present in half (50.0%) of Peru's public pharmacies compared to 89.8% of its private pharmacies ($p = 0.05$). In Nepal, OCS was present in every public pharmacy, while it was present in 70.0% of private pharmacies ($p = 0.283$). OCS was carried by every public and private pharmacy in Uganda that was surveyed [60].

Availability of inhaled corticosteroids

In Nepal (22.2% and 12.7%, and Peru (33.7% and 5.8%, respectively), beclomethasone (WHO-EML) and fluticasone were mainly unavailable. In Nepal, the inhaler for budesonide (WHO-EML) monotherapy was stocked in 41.3% of pharmacies, making it the most widely accessible ICS. There were no ICS available in Uganda, and there were no budesonide data available for Peru. In Peru, public pharmacies (83.3%) had ICS more frequently than private pharmacies (30.6%) ($p = 0.05$). Nepal also possessed the best combination therapy formulations (ICS+LABA, ICS+LAMA, ICS+SABA) [60].

Availability of long-acting beta agonists

In Nepal, only 30.3% of pharmacies carried salmeterol, the medication used in LABA monotherapy. In Nepal, the bulk of public pharmacies (66.6%) carried salmeterol, while 28.3% of private pharmacies carried salmeterol inhalers ($p= 0.17$). In contrast to Peru (6.7%, 7 total pharmacies with at least one), Nepal (87.3%, 55 total pharmacies with at least one combination) had a greater availability of ICS + LABA combination therapies. LABA therapy was not available in any of the Ugandan pharmacies surveyed. In Nepal, at least one ICS + LABA combination therapy was stocked in 88.3% of private pharmacies and 66.6% of public pharmacies, respectively ($p = 0.22$). In Peru, the percentage of private pharmacies that carried ICS + LABA inhalers was 7.1%; public pharmacies did not carry the medication ($p = 0.50$) [60].

Availability of long-acting muscarinic agonists

Only Nepal (77.8%) had access to tiotropium monotherapy (WHO-EML). In Nepal, 66.6% of public pharmacies and 78.3% of private pharmacies carried tiotropium monotherapy ($p = 0.60$). In Nepal, 14.3% of pharmacies carried the combination therapy of formoterol + tiotropium (LABA + LAMA, WHO-EML). In Nepal, 100% of public pharmacies and 13.3% of private pharmacies reported carrying LABA+LAMA inhalers ($p=0.05$). In Nepal, the only LAMA formulations available were generic ones [60].

Side effects

Possible local side effects from corticosteroid inhalation are, cough reflex, oesophageal-oropharyngeal candidiasis, perioral dermatitis, a hoarse voice, having a dry mouth and a thirst, bad breath, or halitosis,

an elevated risk, particularly in adults of tuberculosis, an atypical mycobacterial infection and pneumonia. Possible systemic side effects of inhaled corticosteroids encompass hindrance to linear growth (diminished growth rate leading to shorter final stature), adrenal insufficiency or crisis as a result of suppression of the hypothalamic-pituitary-adrenal axis, implications for bone health such as osteoporosis and susceptibility to bone fractures, effects on immune function, and ocular complications including the development of cataracts and glaucoma. Additionally, there might be impairment in glycemic control [62]. These side effects depend on the type and dosage of ICS used along with how it is administered (e.g., dry powder inhalation (DPI) or metered-dose inhalation (MDI).

Linear growth

Despite the common saying that "being short never caused anyone harm" and the acknowledged ability of inhaled corticosteroids (ICSs) to manage a potentially life-threatening condition, parents' primary worries regarding these medications understandably revolve around the potential impact on their child's growth [63].

Systemically absorbed corticosteroids can influence linear growth through various mechanisms, including the suppression of growth hormone, down-regulation of growth hormone receptors, inhibition of insulin-like growth factor-1, and suppression of collagen synthesis at the epiphyseal growth plate. According to a Cochrane review conducted in 2014, the continual use of inhaled corticosteroids (ICSs) at low to medium daily doses is linked to an average reduction of 0.48 cm/year in linear growth velocity and a 0.61 cm variance in height from baseline over a one-year treatment period in children suffering from mild to moderate persistent asthma [65].

Suppression of the hypothalamic-pituitary-adrenal system

High-dose corticosteroids from external sources can suppress adrenal function through negative feedback mechanisms. This suppression may lead to adrenal insufficiency, which can be overlooked until the body faces additional stress or a reduction in asthma treatment [63]. Previously considered rare, adrenal crises due to inhaled corticosteroid (ICS) use have been reported. Symptoms include fatigue, vomiting, and joint pain, progressing to hypotension and hypoglycaemia if untreated. Risk factors include prolonged use and high doses of ICSs, but even lower doses may cause problems. Co-administration of medications enhancing steroid effects or additional steroid prescriptions heightens the risk. Evaluation for adrenal suppression, preferably by a paediatric endocrinologist using dynamic testing, is crucial for symptomatic and high-risk patients [66]. Management should involve collaboration between paediatric endocrinologists and asthma specialists, emphasizing patient and family education for early recognition and implementation of a rescue plan [64].

Effects on bone health

Systemic glucocorticosteroid use can affect bone health, but studies haven't consistently linked inhaled corticosteroids (ICSs) with fractures or reduced bone density [67]. Recent research found no significant association between ICS use and fractures in asthma patients. However, systemic corticosteroid use was linked to a higher fracture risk. Clinicians should remain cautious, especially with additional risk factors for reduced bone density. Nutritional interventions ensuring sufficient vitamin D and calcium intake are crucial, and monitoring vitamin D levels in asthmatic children is advised [68,69]. Weight-bearing exercises are encouraged, but routine bone density screening isn't recommended for children using ICSs without major risk factors [64].

Complications related to the eyes (cataract and glaucoma)

Because systemic steroids increase the risk of developing cataracts and glaucoma, researchers have looked into whether inhaled steroid therapy has similar effects on the eyes [70]. The CAMP study provided reassurance regarding cataract formation, as only one child out of 311 who received budesonide had a tiny posterior subcapsular cataract [71]. Similarly, there hasn't been an observed increase in glaucoma among children prescribed inhaled corticosteroids [64].

Other side effects including oropharyngeal candidiasis, which occurs in 5-

25% of patients and is characterized by a burning sensation in the mouth and whitish rashes on mucous membranes. The risk of candidiasis is directly related to the dose and frequency of inhaled steroid use. Prevention strategies include rinsing the mouth after each inhalation, using a spacer or powder inhaler, and reducing the dose and frequency of steroid administration during asthma remission [72, 61]. Another potential side effect is dysphonia, observed in 30-58% of patients, particularly those whose professions involve heavy voice use. This condition is attributed to steroid myopathy of the laryngeal muscles due to drug deposition [74]. Treatment options include switching to powder inhalers and decreasing the steroid dose. Irritation of the upper respiratory tract, characterized by cough and bronchospasm, can result from propellants in metered-dose inhalers (MDIS). Prevention methods include using SABA before corticosteroid inhalation, employing a spacer, and switching to powder inhalers [62, 74].

The consumption of inhaled corticosteroids is linked to a notable 34% rise in the chances of risk of incident diabetes, which is defined as the start of anti-diabetic medications, in a large group of COPD and asthma patients [75]. These medicines are often used in treating asthma or COPD, and patients are sometimes given high doses, equivalent to 1000μg of fluticasone daily with a 64% increase the chances of risk [76].Furthermore, a study conducted by David B. Price and others they discovered that inhaled corticosteroids elevates the chances of developing risk to insulin therapy in patients already receiving oral hypoglycaemic agents for diabetes by 34%, and higher doses increased this risk of chances by 54% [77].

To manage systemic side effects of inhaled corticosteroids (ICS) in asthma patients, it's advised to prescribe the lowest effective ICS dose to maintain asthma control while minimizing adverse effects. Regular monitoring for signs of systemic side effects, such as cataracts, glaucoma, osteoporosis, and pneumonia, is crucial. Treatment plans should be tailored to each patient's needs, considering comorbidities and age-related factors that may impact systemic side effect risk. When systemic side effects are significant, alternative asthma medications or treatment approaches may be considered, particularly for elderly patients. Educational programs aimed at increasing awareness of ICS benefits and risks can enhance their appropriate use. Implementing these management strategies can optimize asthma treatment with ICS in elderly patients while mitigating systemic side effect risks.

CONCLUSION

This review emphasizes the need for a comprehensive asthma management approach, integrating pharmacology, genetics, and improved healthcare delivery. This review highlights the historical evolution of asthma, from the use of smoke inhalation to modern inhalers,and the use of ICS and beta-2 adrenergic receptor agonists, addressing cost and medication accessibility. It emphasizes the potential of pharmacogenomics in customizing treatment based on genetic variations, while also addressing ICS side effects and proposing risk mitigation strategies. Adopting a holistic approach, the strategy aims to improve asthma control, reduce exacerbations, and elevate global patient outcomes. Integration of pharmacogenomic and clinical data enables tailored therapeutic approaches, advancing precision medicine in asthma care and enhancing patient quality of life. The review emphasizes delayed specialist referrals for complex asthma cases and provides revised treatment guidelines across severity levels, stressing tailored considerations in resource limited settings. Ultimately, it promotes for global asthma care challenges.

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