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Asthma Management: Current Guidelines and Treatment Strategies for Asthma Control

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ABSTRACT

Asthma is a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The pathophysiology involves various cells and cellular components, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. This inflammation leads to widespread but variable airflow obstruction and increased bronchial sensitivity to a range of stimuli. Asthma affects over 330 million people worldwide, with prevalence rates varying widely between countries. Epidemiological studies have shown increasing prevalence in developing nations adopting Westernized lifestyles and among children with allergic sensitization and multimorbidity. The diagnosis of asthma is based on a probabilistic assessment of symptoms and fluctuating expiratory airflow limitation, as no definitive diagnostic standard exists. Differential diagnoses and comorbidities, such as rhinitis, rhinosinusitis, obesity, obstructive sleep apnea, and gastroesophageal reflux disease, should be evaluated and managed appropriately. The management of asthma involves a stepwise approach, with inhaled corticosteroids (ICS) being the cornerstone of maintenance therapy. Long-acting β2-agonists (LABAs) are recommended in combination with ICS

for patients with inadequately controlled asthma. Other treatment options include leukotriene modifiers, long-acting muscarinic antagonists (LAMAs), and targeted biological therapies for severe, uncontrolled asthma. Short-acting ß2-agonists (SABAs) are no longer considered the best sole therapy for intermittent asthma, and formoterol in combination with ICS is now recommended for as-needed use. Non-pharmacological interventions, such as avoiding triggers, maintaining a healthy lifestyle, and considering bronchial thermoplasty in select cases, may also play a role in asthma management.

KEYWORDS: Asthma, asthma management, asthma diagnosis.

1. Introduction

Asthma is a persistent inflammatory condition affecting the airways, where various cells and cellular components are involved, notably mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In those who are susceptible, this inflammation leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly during the night or early morning hours. These episodes are commonly associated with widespread but variable airflow obstruction, which is frequently reversible either spontaneously or with intervention. Furthermore, the inflammation contributes to an enhanced bronchial sensitivity to a range of stimuli. In some asthma patients, however, reversibility of airflow limitation may be incomplete. This definition, much like that of chronic sinusitis, emphasizes the presence of inflammation and resultant symptoms without specifying the cause, which remains incompletely understood, or the variable course of the disease (Lung & Institute, n.d.).

Epidemiology

Asthma affects over 330 million people worldwide throughout their education and work years, with exacerbations imposing a substantial burden on productivity (Vos et al., 2012). The rate of self-reported asthma differs widely between countries, ranging from 0-2% in China to as high as 21% in Australia, with a global average of 4.5% (To et al., 2012). More pronounced disparities were observed in the International Study of Asthma and Allergies in Childhood (ISAAC) study among children and adolescents, revealing an overall prevalence of 10% in the European Union and North America (Gibson et al., 2013). While epidemiological data vary, it is widely acknowledged that asthma prevalence is steadily rising in developing nations adopting more Westernized lifestyles, with similar trends seen in parts of Europe and Australia (Anandan et al., 2010).

Due to the significant economic and health burden posed by chronic respiratory diseases, a public health policy document was directed toward the Council of the European Union. This document included initiatives on early detection, prevention, efficient care, and new therapeutic targets for allergic diseases and asthma (Samoliński et al., 2012).

Childhood asthma is characterized by a predominance of allergic sensitization and multimorbidity, especially in males; however, this gender pattern often reverses during adolescence (Gabet et al., 2016). Recently, a comprehensive review of

systematic reviews in allergy epidemiology identified asthma as the most frequently reviewed allergic disease (Genuneit et al., 2017). Over the past two decades, significant increases have been noted in allergic sensitization among children, which may contribute to a higher prevalence of allergic asthma in future years (Rönmark et al., 2009). Indoor allergen exposure, multimorbidity related to allergies, and/or polysensitization have been strongly linked to the development and persistence of asthma (Murray et al., 2001). Multiple pediatric cohort studies have also found that the coexistence of other allergic conditions significantly raises the risk of developing asthma later in life (Gough et al., 2015). In school-aged children, causal network analysis has shown that allergen sensitization, allergic inflammation, and rhinitis activity explain more than half of the variance in asthma severity (Liu et al., 2016).

In adults, the prevalence of allergic asthma has increased steadily from 1996 to 2006 and again by 2016, while non-allergic asthma rates have remained stable (Backman et al., 2017). Additionally, polysensitization has been positively linked with asthma incidence (Toppila-Salmi et al., 2015), and more recently, adult-onset asthma has shown a dose-dependent association with the number of allergic comorbidities, particularly at younger ages (Toppila-Salmi et al., 2019).

The role of exposure to specific environmental factors in asthma and allergy development, such as indoor allergens, dampness, and mold, has also been highlighted in certain populations, including immigrants and farming communities (Radhakrishnan et al., 2019). More recent research has documented the impact of in utero and early life exposures on asthma development and sensitization (Lundbäck et al., 2016).

Pathophysiology and mechanisms

The connection between asthma and inflammation has been recognized for over 50 years (Mosmann et al., 1986). The currently accepted "classical" immunopathogenic model of asthma centers on CD4+ Th2 cells as key players in the adaptive immune response, promoting eosinophilic airway inflammation by stimulating the release of interleukins (IL)-4, IL-5, and IL-13 in response to specific allergens (Kuruvilla et al., 2019). IL-4 functions as an upstream cytokine, binding to the IL-4R α receptor and modulating Th0 cells' differentiation into Th2 cells and the proliferation of T-regulatory cells (Gandhi et al., 2017). IL-5 facilitates the development, maturation, activation, and mobilization of eosinophils, as well as influences the development and function of mast cells and basophils (Rosenberg et al., 2007). Additionally, IL-13 plays a multifaceted role in asthma by driving B-cell isotype switching, mucus overproduction, goblet cell hyperplasia, subepithelial fibrosis, and airway hyperresponsiveness (AHR) (Akdis et al., 2016). This understanding led to the classification of asthma into T2 high (eosinophilic) and Th2 low (non-eosinophilic) endotypes (Sterk & Lutter, 2014). Th2 high and low asthma phenotypes often show varied therapeutic responses, with non-Th2-driven asthma patients often responding poorly to steroids. Further research revealed significant heterogeneity within asthma, with various inflammatory pathways impacting its endotypes. Recently, it has been recognized that multiple cell types, including invariant T cells, natural killer cells, eosinophil/basophil progenitors, Th1 cells in certain contexts, and Type 2 innate

lymphoid cells (ILCs), contribute cytokines in the Th2 high endotype (Robinson et al., 2017). Consequently, type-2 inflammation has emerged as a key mechanism, while type-2 low asthma includes several disease endotypes, each affecting smaller patient subgroups.

A newly identified subset of innate immune cells, innate lymphoid cells (ILCs), has been characterized. There are three groups of ILCs: ILC1 and ILC3 primarily produce interferons and IL-17/IL-22, respectively, while ILC2 generates significant quantities of Th2-like ILs, such as IL-4, IL-5, and IL-13. These cytokines activate mast cells, basophils, eosinophils, and promote IgE antibody production, leading to allergic airway inflammation (Annunziato et al., 2015; Halim et al., 2012). Though ILC2 cells lack antigen-specific receptors, they are activated by epithelial cell-derived mediators in response to proteases, such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP), also called alarmins (Peebles & Aronica, 2019). Specifically, IL-33 plays a central role in ILC2 cytokine production, while also inducing IL-5+ CD4+ T cells independently of IL-4 and enhancing the pro-allergic properties of CD4 T cells (Morita et al., 2017). In asthma patients, higher levels of IL-33 and TSLP are inversely correlated with lung function (Momen et al., 2017), and increased IL-25 mRNA expression in airway samples is significantly linked to bronchial hyperresponsiveness and eosinophilic activation (Cheng et al., 2014). Moreover, virus-related IL-33 and IL-25 responses in ILC2 cells have been identified as critical determinants and potential therapeutic targets during virus-induced asthma exacerbations, which significantly contribute to asthma morbidity (Andreakos & Papadopoulos, 2014).

Another significant pathway in asthma pathogenesis involves CD4 Th17 cells, which produce IL-17A and IL-17F. These cytokines stimulate the production of other cytokines and chemokines that support neutrophil recruitment and survival in the airway and lungs (Veldhoen, 2017). Both animal and clinical studies indicate that IL-17A amplifies Th2-driven airway hyperreactivity and inflammation and promotes airway smooth muscle proliferation, with a significant association observed between IL-17A and asthma severity (Barlow et al., 2011; Chang et al., 2012).

In addition, lipid mediators, particularly eicosanoids like prostaglandins (PG) such as PGD2, cysteinyl leukotrienes (LTs), and thromboxanes, play a role in asthma pathogenesis (Kytikova et al., 2019). These are derived from arachidonic acid, released from cell membranes of degranulated mast cells and basophils, and contribute to smooth muscle constriction and inflammatory responses that aggravate allergic reactions. PGD2, primarily produced by mast cells and eosinophils, has been linked to asthma control levels, frequency of exacerbations, and markers of Th2 inflammation. Current studies are exploring the use of PGD2 antagonists in managing uncontrolled asthma (Erpenbeck et al., 2016; Fajt et al., 2013).

Cysteinyl LTs are produced primarily by eosinophils, basophils, mast cells, and macrophages in response to specific stimuli such as IgE, IgG complexes, endotoxins, and phagocytosis (Sirois, 2019). The binding of LTs to their receptors triggers bronchoconstriction, mucus production, and airway edema, resulting in increased pulmonary resistance and decreased lung compliance.

Recent advancements in lipidomics have uncovered a new group of bioactive lipid

mediators with pro-resolving capabilities, including maresins, lipoxins, resolvins, and protectins (Serhan & Levy, 2018). These molecules are involved in restoring homeostasis following airway inflammation and are now being investigated as potential immune-resolvent therapies (Kytikova et al., 2019).

Mechanisms underlying the persistence and remodeling in allergic asthma are not yet fully understood. In vitro and in vivo research highlights the role of atopy and allergic inflammation in the onset and maintenance of respiratory allergies. Early in vitro models indicated that infections by human rhinovirus (hRV) a major trigger of asthma exacerbations impair epithelial repair, thus prolonging inflammation (Bossios et al., 2005). Additionally, hRV infections promote airway remodeling through angiogenesis, mediated by vascular endothelial growth factor (VEGF), with effects amplified in the presence of atopy (Psarras et al., 2006). Similar responses are noted for other profibrotic factors such as fibroblast growth factor 2 (Skevaki et al., 2012) and transforming growth factor (TGF)-β (Bielor et al., 2017). Clinical studies indicate that hRV-triggered asthma exacerbations are more frequent among those with high IgE levels to relevant allergens, highlighting the importance of the host's atopic status (Soto-Quiros et al., 2012). Moreover, the duration of airway hyperresponsiveness a marker of asthma severity and inflammation is significantly extended in atopic individuals experiencing frequent colds, which may contribute to prolonged inflammation and symptom persistence (Xepapadaki et al., 2005). This observation has led to the hypothesis that repeated infection-driven events may alter innate, adaptive, and/or regulatory immune responses toward chronic inflammation. Findings from the PreDicta childhood cohort suggest a unique humoral response in asthmatic individuals, differing from healthy controls, which impacts immunity against various RV species (Megremis et al., 2018).

More recently, the complex role of the airway and gut microbiomes in asthma's development and severity has gained recognition (Sullivan et al., 2016). Studies show that early-life microbial colonization is strongly associated with asthma risk in preschool years (Bisgaard et al., 2007), while airway bacterial load correlates with asthma phenotypes, disease activity, and airway hyperresponsiveness (Durack et al., 2017). Additionally, the role of the virome is being explored in the context of asthma pathogenesis and exacerbations (Megremis et al., 2018).

Diagnosis

No definitive diagnostic standard exists for asthma. The diagnosis is based on a probabilistic assessment that considers both symptoms and fluctuating expiratory airflow limitation. Asthma is a heterogeneous condition, and either one or both of these features may be absent in some patients.

Various factors can influence the likelihood that symptoms are attributable to asthma. In pediatric cases, accurately assessing symptoms and rescue β2 agonist use can be challenging, as most of the information is provided by parents, who may not always be present with their child and thus might lack awareness of key details. Play is crucial for a child's normal social and physical development, yet physical activity frequently triggers asthma symptoms, leading children to avoid intense play or exercise to prevent symptom onset. Many parents and healthcare providers are

unaware of this avoidance behavior, making it essential to thoroughly review the child's daily activities, including their enthusiasm for play and sports participation, especially when parents report irritability, fatigue, and mood changes as the main concerns.

Fluctuating expiratory airflow limitation is characterized by variability that exceeds the normal range observed in healthy individuals, typically associated with a forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio that falls below predicted levels based on age, sex, height, and race. This variability can be assessed in several ways. First, bronchodilator reversibility is demonstrated by an increase in FEV1 of more than 12% and at least 200 mL (more than 12% of predicted in children) within 10–15 minutes following administration of a rapid-acting β2 agonist, indicating abnormal variation. However, a negative result does not exclude asthma. Second, a bronchial provocation test is often used, with an exercise challenge being the most common in pediatric cases. Exercise challenges can be difficult to execute correctly in general practice, but if the heart rate exceeds 180 beats per minute during the final 3 minutes of an 8-minute test, most children with exercise-induced asthma will produce a positive result (Joos et al., 2003). A negative result, however, does not rule out asthma. There is ongoing debate regarding the criteria for a positive exercise challenge. GINA guidelines (2017) suggest that a decrease in FEV1 of more than 10% of the predicted value and over 200 mL in adults, or more than 12% of predicted in children, is indicative of asthma (Brouwer et al., 2008; Pellegrino et al., 2005). In both adults and children, a decrease in FEV1 of at least 20% with direct challenge drugs (methacholine and histamine) or at least 15% with indirect challenge drugs (hypertonic saline, eucapnic hyperventilation, and mannitol) supports an asthma diagnosis, though these tests are less commonly administered to children. Proper performance of any challenge test is critical to avoid false positives, and confirmation of a reduced FEV1 to FVC ratio is required to rule out other factors like variable inspiratory effort or upper airway dysfunction.

Additionally, within-day variability in peak expiratory flow (PEF), expressed as amplitude percent mean, of over 10% (greater than 13% in children) can indicate fluctuating airflow limitation. Week-to-week variability in lung function, estimated at around 11–12% in adults and children, makes tests such as FEV1 differences of more than 12% (and greater than 200 mL in adults) between visits or following 4 weeks of anti-inflammatory treatment somewhat unreliable.

The probability of asthma increases with greater and more frequent airflow variability. However, airflow limitation may not always be present, and documenting it is more likely during or shortly after symptoms. While variable airflow limitation alone is insufficient to diagnose asthma as it may also be present in chronic obstructive pulmonary disease (COPD) or in asymptomatic individuals with airway hyper-responsiveness excessive variability typically persists in children but may diminish in long-standing asthma in adults (McGeachie et al., 2016; Vonk et al., 2003).

Differential diagnosis

To confirm an asthma diagnosis, it is essential to evaluate potential alternative diagnoses or associated comorbidities. When underdiagnosed or inadequately

managed, comorbid conditions can significantly impact both quality of life and asthma control (Boulet, 2009). Rhinitis and rhinosinusitis, with or without nasal polyps (and rhino conjunctivitis in children), are the most frequently observed asthma comorbidities and are often linked with poorly controlled asthma (Dixon et al., 2006).

Obesity is associated with exertional dyspnoea due to its effects on functional residual capacity and expiratory reserve volume. In adults, particularly women, obesity may be linked with refractory asthma, characterized by a lower eosinophilic and a higher neutrophilic sputum profile (Chung et al., 2014).

Obstructive sleep apnoea (OSA) is prevalent in adults with asthma, particularly when asthma is severe. In children, symptoms such as tiredness, irritability, and difficulty in concentrating are common indicators of poorly controlled asthma. However, if these symptoms persist despite adherence to treatment, obstructive sleep apnoea should be considered (van Maanen et al., 2013).

Gastro-oesophageal reflux disease (GERD) is observed in 25–80% of both adults and children with asthma. Potential mechanisms involve increased acid reflux during asthma exacerbations with hyperinflation, micro aspirations that trigger neurogenic inflammation, and β2 agonists that lower oesophageal sphincter pressure. In adults, symptomatic GERD (diagnosed via 24-hour pH monitoring) is associated with reduced quality of life (Parsons & Mastronarde, 2010). In children, however, data regarding GERD's impact remain limited.

Asthma–COPD overlap is a provisional term describing adult patients exhibiting both functional and clinical characteristics of asthma and chronic obstructive pulmonary disease (COPD), such as persistent airflow limitation. Outcomes for these patients including symptoms, quality of life, exacerbation rates, hospitalizations, and mortality are worse than for asthma or COPD alone. The prevalence of this overlap condition increases with age and is more common in smokers, although nonsmokers with asthma may also experience accelerated lung function decline and develop persistent airflow limitations, despite typical asthma pathology (Bateman et al., 2015).

Mental health disorders, including anxiety, depression, and panic attacks, are more frequently observed in asthma patients of all severities and have an adverse effect on quality of life. Anxiety symptoms such as hyperventilation, dyspnoea, and cough may mimic asthma exacerbations. Psychological stress may contribute to poor treatment adherence, increased airway inflammation, and worsened asthma control. Children with asthma, along with their families, commonly experience depression and anxiety (ten Brinke et al., 2001).

Asthma in children is associated with an increased risk of poor health, reduced physical activity, lower fitness, avoidance of social interactions, and lower academic performance, particularly in mathematics and reading, especially when asthma is severe or poorly controlled (O'Byrne et al., 2013). Although associations between asthma and academic performance are less consistent, increased school absenteeism is well documented, though it does not appear to correlate with asthma severity or

control.

High-dose inhaled corticosteroids are associated with local side effects such as oral candidiasis (occurring in approximately 5–10% of patients), dysphonia, and xerostomia. In adults, systemic side effects, including an increased risk of diabetes and poor glycaemic control, glaucoma, cataracts, bruising or purpura, adrenal insufficiency, and osteoporosis are more common with long-term use of high-dose inhaled corticosteroids or systemic corticosteroids.

For children, standard inhaled corticosteroid doses typically do not result in clinically significant systemic adverse effects. However, the use of systemic corticosteroids or oral corticosteroids does increase the risk of fractures in a dose-dependent fashion. Higher doses of inhaled corticosteroids may lead to growth delay within the first year of treatment, though this effect is not cumulative or progressive. Only one study has indicated an impact on final adult height, with a reduction of less than 0.7% (Kelly et al., 2012). Poorly controlled asthma can also have negative effects on growth (Pedersen, 2001).

Management

Asthma management and treatment objectives can be categorized into two primary areas: achieving asthma control and reducing future risks associated with both the disease and its treatments. Effective asthma control entails minimizing daytime and nighttime asthma symptoms, optimizing lung function, limiting the use of short-acting β2-agonists (SABAs) for quick relief, and enabling patients to maintain regular daily activities. Additionally, it is essential to reduce the likelihood of asthma-related mortality, exacerbations, impaired lung growth (in children) or lung function (in adults), and adverse effects from asthma medications. As a chronic disease, asthma requires ongoing assessment, adjustments to therapy, and regular evaluation of treatment response (Selroos et al., 2015). It is also crucial to consider patient preferences and practical considerations. Therefore, international guidelines advocate for a stepwise approach in asthma treatment, which involves “stepping-up” therapy if adequate asthma control is not sustained over time and “stepping-down” therapy if control is achieved and exacerbations are minimized. Importantly, adherence to treatment, correct inhaler use, and the presence of comorbidities should always be reviewed before modifying the treatment plan.

As robust research evidence emerges, recommended treatment approaches continue to evolve. The 2019 Global Initiative for Asthma (GINA) report highlighted the importance of inhaled corticosteroid (ICS)-based controller therapy, used either as-needed or on a regular basis, for adults and adolescents with asthma (Rajan et al., 2020). When needed, increasing the ICS dosage or adding other medications are the preferred next steps. Additionally, SABAs are no longer recommended as the first-line reliever. For children aged 6–11 years, a daily low-dose ICS is the recommended starting treatment, with dose increases or additional medications considered as necessary. In younger children (≤5 years), diagnosing asthma remains challenging. In this age group, there is still limited understanding of the role of different phenotypes and endotypes, as well as the relationship between preschool wheeze a common feature of pediatric asthma and the later onset of asthma (Papadopoulos et al., 2019). In these patients, escalating doses of ICS are the preferred controller

therapy (GINA report 2019).

Inhaled Corticosteroids

Inhaled corticosteroids (ICSs) are widely recognized as the cornerstone of maintenance therapy for asthma, offering the most effective anti-inflammatory treatment across all age groups and levels of disease severity. Available devices include pressurized metered-dose inhalers (pMDIs), which can be used with or without a spacer, dry powder inhalers (DPIs), and nebulizers. Selecting the appropriate device depends on patient factors such as respiratory function, age, personal preferences, and ability to use the device effectively. Proper inhaler technique requiring patient education and regular assessment is crucial, as is adherence to treatment, both of which are key to minimizing exacerbation risks and managing symptoms. A recent systematic review found that, although some interventions improve inhaler technique in specific situations, evidence is limited regarding the most effective methods and their measurable impacts on clinical outcomes (Normansell et al., 2017). Numerous randomized controlled trials (RCTs) have investigated the relative efficacy of ICSs. Fluticasone, for example, administered at the same or half the daily dose of budesonide or beclomethasone, resulted in modest improvements in some lung function measures across various drug dosages, age groups, and device types (Adams et al. 2007). No notable differences were found in terms of exacerbations, SABA use, or symptom relief (Adams et al. 2007). Guidelines suggest a daily low dose of ICS for adults and children with persistent asthma. No clinically relevant differences were observed in lung function, exacerbation risks, rescue medication use, or symptom control between patients started on low, moderate, or high ICS doses (Powell & Gibson,. 2004). For those who do not achieve adequate control, options include dose escalation or adding another controller medication. Conversely, evidence on the ideal timing for reducing ICS doses in well-controlled adult asthma is limited (Crossingham et al., 2017). Studies and reviews have also focused on ICS use at the onset of exacerbations in school-age children with asthma and preschoolers with recurrent wheezing. Children with intermittent ICS use did not differ significantly in oral corticosteroid use or severe health events compared to regular ICS users; however, daily ICS improved lung function, asthma control, and airway inflammation markers (Chauhan et al., 2013). Long-term corticosteroid use raises concerns regarding side effects; although ICSs are generally associated with fewer and less severe adverse effects, extended use increases the risk of systemic effects, particularly in children and the elderly. Local side effects (e.g., oral thrush, hoarseness) and systemic effects (e.g., adrenal suppression, cataracts, osteoporosis) may occur. ICS use has been linked to a minor reduction in growth velocity in children, following a dose-dependent trend (Zhang et al. 2014). Additionally, the presence of comorbidities like allergic rhinitis or atopic dermatitis can increase the cumulative corticosteroid dose from various delivery routes. Therefore, patients on high-dose ICS therapy for extended periods should be regularly monitored for early signs of adverse effects.

ICS/LABA Combination

Long-acting β2-agonists (LABAs) approved for asthma treatment include salmeterol, formoterol, and the ultra-long-acting vilanterol (24-hour action duration), while indacaterol and olodaterol are approved for COPD use. LABAs are recommended in combination with ICS as the next step for patients aged >5 years whose asthma is inadequately controlled with low-to-medium ICS doses (GINA report 2019). This combination reduces exacerbation risks, enhances lung function, and improves asthma symptoms compared to ICS alone in adults (Ducharme et al. 2010). However, adding LABA to ICS in children has not shown a reduction in exacerbations requiring systemic steroids compared to ICS alone, though it improved other asthma control measures (Chauhan et al. 2015). A single inhaler serving both as controller and reliever, known as "Single Inhaler Therapy" (SiT) or "Single Maintenance and Reliever Therapy" (SMART), has gained popularity due to convenience and potential adherence benefits. For adults and adolescents, the budesonide/formoterol SiT reduced exacerbations needing systemic steroids or hospital admission compared to high-dose ICS/LABA inhalers and as needed SABA (Kew et al. 2013). Recent RCTs examined budesonide/formoterol use as needed in adults and adolescents with mild asthma ((Bateman et al., 2018; Beasley et al., 2019; O'Byrne et al., 2018)et al. 2018; O'Byrne et al. 2018; Beasley et al. 2019). Exacerbation rates were similar between the as-needed budesonide/formoterol group and the daily budesonide/as-needed SABA group, with daily budesonide providing better symptom control. Patients using as-needed budesonide/formoterol had fewer exacerbations and improved symptom control compared to as-needed albuterol or terbutaline, along with reduced glucocorticoid exposure. Based on these findings, GINA now recommends as-needed ICS/formoterol as the preferred reliever for all asthma severity levels in adults and adolescents (GINA report 2019). LABAs should not be used as monotherapy due to increased morbidity and mortality risks; however, evidence from current fixed-dose combination inhalers has been reassuring, and the FDA has determined that ICS/LABA combinations do not elevate serious asthma-related risks compared to ICS alone.

Leukotriene Modifiers

Leukotriene modifiers include three leukotriene receptor antagonists (LTRAs) montelukast, zafirlukast, pranlukast and the 5-lipoxygenase inhibitor zileuton. While availability varies globally, montelukast is the most commonly used, with zafirlukast also utilized in the United States. These agents are used in mild asthma as an alternative to ICS and in more severe asthma as an alternative to increasing ICS doses or adding LABAs (GINA report 2019). For adults and adolescents with mild persistent asthma, LTRA monotherapy was more effective than placebo in reducing exacerbations and improving asthma control and quality of life (Miligkos et al., 2015). However, LTRAs generally show less efficacy than ICSs in both adults and children, with higher exacerbation rates, worsened lung function, and poorer symptom and quality-of-life outcomes (Chauhan & Ducharme,. 2012). In adults and adolescents, LTRAs as an add-on to ICS were evaluated against the same, increased, or reduced ICS dose, showing that LTRAs as add-ons reduced exacerbation risks and improved lung function and asthma control but did not outperform higher or reduced ICS doses (Chauhan et al., 2017). LTRAs used as second-line therapy were less

effective than LABAs in lung function tests and were associated with a significant, though comparable, increase in exacerbation risk (Chauhan & Ducharme,. 2014). For preschool children with asthma or recurrent wheezing, LTRA maintenance treatment is generally less effective than ICS (Castro-Rodriguez et al., 2018). RCTs suggest that LTRAs have a safety profile comparable to placebo or active drugs (Miligkos et al., 2015). The convenience of once- or twice-daily oral dosing and potential efficacy in patients with specific conditions (e.g., allergic rhinitis, young children) make LTRAs a viable option, especially for patients who are unwilling or unable to use ICS.

Long-Acting Muscarinic Antagonists

Long-acting muscarinic antagonists (LAMAs) are recommended for difficult-to-manage asthma as add-ons to ICS or as an alternative to ICS/LABA combinations. Tiotropium, delivered via a mist inhaler, is approved for use in asthma patients aged ≥6 years. In five RCTs involving 2,563 adult asthma patients, tiotropium combined with ICS reduced exacerbation risks and improved lung function, although evidence for other efficacy measures remains inconclusive (Anderson et al., 2015). When compared to salmeterol or formoterol as an add-on to ICS in about 2,000 adults, tiotropium did not reduce exacerbations but did yield modest improvements in certain lung function measures. Tiotropium added to ICS/LABA in adult asthma patients has also shown minor additional benefits (Kew & Dahri, 2016).

Biologicals

Several targeted therapies are now available, with more in development, aimed at patients whose asthma remains uncontrolled despite optimal inhaler therapy. Omalizumab, the first monoclonal antibody targeting IgE, received regulatory approval around 15 years ago and has demonstrated efficacy as an adjunct to inhaled corticosteroids (ICS) in reducing exacerbation frequency and enhancing symptom control and quality of life in children aged six years and older and in adults with severe, uncontrolled asthma. Additionally, omalizumab has the potential to concurrently manage other allergy-associated conditions, such as allergic rhinitis and severe food allergies, making it an attractive option for asthma treatment (Humbert et al., 2019). Three additional monoclonal antibodies targeting IL-5 or its receptor mepolizumab, reslizumab, and benralizumab are approved for adults, adolescents (reslizumab, benralizumab), and children over six years (mepolizumab) with severe eosinophilic asthma. These treatments have been shown to reduce severe exacerbations and improve lung function and asthma control markers when compared to placebo (Pavord et al., 2012; Ortega et al., 2014; Castro et al., 2015; Bleecker et al., 2016; FitzGerald et al., 2016). Notably, mepolizumab and benralizumab have demonstrated a capacity to reduce reliance on oral corticosteroids in patients needing systemic steroids to manage their asthma (Bel et al., 2014; Nair et al., 2017b). In 2019, dupilumab, a monoclonal antibody targeting the IL-4 receptor, was approved for adolescents and adults with moderate-to-severe eosinophilic asthma or steroid-dependent asthma. Patients on dupilumab showed fewer severe exacerbations and improved lung function and asthma control compared to those on placebo, with the most notable benefits seen in patients with high baseline eosinophil

counts (Castro et al., 2018). Additionally, in corticosteroid-dependent patients, dupilumab significantly reduced oral steroid use compared to placebo (Rabe et al., 2018). While limited evidence is currently available, no serious adverse effects have been reported for these biologics, making them an important option for managing severe uncontrolled asthma, particularly in patients with a predominantly Th2 inflammatory profile. However, there remains a subgroup of patients with non-Th2 asthma who do not respond adequately to existing standard or targeted therapies. Ongoing trials are exploring other potential therapies, including those targeting additional interleukins (e.g., brodalumab, tezepelumab, RGN3500), prostaglandin D2 receptor inhibitors (fevipiprant), and KIT receptor tyrosine kinase inhibitors (imatinib), with early promising results that await further validation (Corren, 2019).

Systemic Corticosteroids

Systemic corticosteroids are a cornerstone treatment for moderate-to-severe asthma exacerbations. However, in cases where asthma remains uncontrolled despite optimal management and adherence to inhaler therapy, regular systemic corticosteroid use may be required. Long-term systemic corticosteroid therapy is associated with serious adverse effects and should be reserved as a last resort.

Other

Less frequently used controller medications include theophylline and cromones (nedocromil and cromoglycate). Theophylline, an oral bronchodilator, is less effective than ICSs (Dahl et al., 2002) or LABAs (Tee et al., 2007) and poses a risk for severe adverse effects, including cardiovascular and neurological toxicity (Cooling, 1993). Cromones are inhaled drugs with a favorable safety profile but are generally considered to be less effective than low-dose ICS for asthma in both adults and children (Guevara et al., 2006; Sridhar and McKean, 2006).

Allergen Immunotherapy

Allergen immunotherapy (AIT) is a treatment that induces tolerance to specific allergens through repeated exposure to the allergen and may provide benefits for patients with allergic asthma. In 2019, the European Academy of Allergy and Clinical Immunology (EAACI) issued guidelines on house dust mite (HDM) immunotherapy as an add-on for HDM-induced asthma in children and adults (Agache et al., 2019). Two main administration routes are evaluated in these guidelines: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). HDM-SCIT is recommended as an adjunct for symptom and medication reduction in controlled HDM-induced asthma in both children and adults, although evidence remains insufficient to make recommendations regarding exacerbation rates, lung function, or asthma control markers (Agache et al., 2019). HDM-SLIT drops are similarly advised as an adjunctive therapy for controlled HDM-induced asthma in children to help manage symptoms and reduce medication needs (Agache et al., 2019). For adults with controlled or partially controlled HDM-driven asthma, HDM-SLIT tablets are suggested based on moderate-quality evidence as an add-on to regular medication to reduce exacerbations and improve asthma control (Agache et al., 2019). HDM-AIT is contraindicated in patients with uncontrolled asthma due to limited safety data in this group. Overall, AIT shows significant benefits in

selected patients with allergen-triggered asthma (Dhami et al., 2017). However, generalizability is limited due to publication bias, adverse events, and variability in clinical and methodological aspects among published systematic reviews (Abramson et al., 2010; Dhami et al., 2017).

Reliever Medications

For years, short-acting beta-2 agonists (SABAs) have been the preferred choice for managing acute asthma symptoms. Traditional SABAs, such as salbutamol and terbutaline, as well as the rapid-onset long-acting beta-2 agonist formoterol, were prescribed to patients with intermittent asthma as-needed to address bronchospasm symptoms (GINA, 2018; NAEPP EPR3, 2007). However, evidence suggesting that even mild asthma can lead to severe exacerbations or progressive lung function decline, coupled with excessive SABA use by many patients, has shifted treatment guidelines (GINA, 2019). Now, SABAs are no longer considered the best sole therapy for intermittent asthma and are not the preferred reliever for most other asthma patients. Formoterol, with its rapid onset, is now recommended in combination with ICS for as-needed use in patients with intermittent or persistent asthma (GINA, 2019). Additionally, the anticholinergic agent ipratropium is often used in the hospital setting for acute asthma episodes, though its benefit over SABA alone remains unclear (Vezina et al., 2014).

Non-Pharmacological Interventions

In managing chronic conditions like asthma, multiple factors can contribute to exacerbations, warranting consideration of various strategies beyond pharmacological treatments, though evidence is limited for most. Strategies include avoiding smoke, allergens, occupational exposures, and medications like NSAIDs; maintaining a healthy lifestyle (e.g., diet, weight, physical activity); and ensuring vaccinations, particularly for pneumococcal and influenza prevention. Bronchial thermoplasty, a treatment using radiofrequency pulses on the airways, is an option for carefully selected adults with poorly controlled asthma despite optimal pharmacotherapy.

2. Conclusion

asthma management requires a personalized, stepwise approach using inhaled corticosteroids (ICS) as foundational therapy, progressing to combination treatments with long-acting β2-agonists (LABAs), leukotriene modifiers, or biological therapies for severe cases. Recent guidelines Favor ICS-formoterol combinations over short-acting β2-agonists (SABAs) as needed, reflecting evolving strategies. For severe eosinophilic asthma, targeted biologicals offer promising results, though options for non-Th2 inflammation remain limited. Allergen immunotherapy and lifestyle adjustments complement pharmacologic treatments, aiming to improve control, reduce exacerbations, and minimize side effects. Ongoing patient monitoring, education, and adherence are essential to achieving optimal asthma management.

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