



# Type 2 inflammation in asthma and other airway diseases

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**Asthma is a heterogenous disease. Targeted therapies have been developed based on the pathophysiology of type 2 inflammation. These therapies offer hope for improved management of type 2 inflammatory airway diseases.** <https://bit.ly/3HCkrvQ>

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## Abstract

Chronic inflammatory airway diseases, including asthma, chronic rhinosinusitis, eosinophilic COPD and allergic rhinitis are a global health concern. Despite the coexistence of these diseases and their common pathophysiology, they are often managed independently, resulting in poor asthma control, continued symptoms and poor quality of life. Understanding disease pathophysiology is important for best treatment practice, reduced disease burden and improved patient outcomes.

The pathophysiology of type 2 inflammation is driven by both the innate immune system triggered by pollutants, viral or fungal infections involving type 2 innate lymphoid cells (ILC2) and the adaptive immune system, triggered by contact with an allergen involving type 2 T-helper (Th2) cells. Both ILC2 and Th2 cells produce the type-2 cytokines (interleukin (IL)-4, IL-5 and IL-13), each with several roles in the inflammation cascade. IL-4 and IL-13 cause B-cell class switching and IgE production, release of pro-inflammatory mediators, barrier disruption and tissue remodelling. In addition, IL-13 causes goblet-cell hyperplasia and mucus production. All three interleukins are involved in trafficking eosinophils to tissues, producing clinical symptoms characteristic of chronic inflammatory airway diseases.

Asthma is a heterogenous disease; therefore, identification of biomarkers and early targeted treatment is critical for patients inadequately managed by inhaled corticosteroids and long-acting  $\beta$ -agonists alone. The Global Initiative for Asthma guidelines recommend add-on biological (anti IgE, IL-5/5R, IL-4R) treatments for those not responding to standard of care. Targeted therapies, including omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab, were developed on current understanding of the pathophysiology of type 2 inflammation. These therapies offer hope for improved management of type 2 inflammatory airway diseases.

## Introduction

Asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) are mainly type 2 inflammatory diseases which, when left uncontrolled, are characterised by debilitating symptoms, including shortness of breath, airway obstruction (asthma) or nasal obstruction, loss of smell, and nasal discharge (CRSwNP) [1, 2]. Persistent type 2 inflammation continuously damages the epithelium, creating a vicious cycle whereby the inflammatory response escalates, exacerbating the already debilitating clinical symptoms [3]. These



conditions are often managed as single entities, yet their coexistence is common and linked with a shared pathological mechanism. People with allergic asthma can commonly present with allergic rhinitis, and patients with rhinosinusitis with nasal polyps often have comorbid asthma [4]. These comorbidities are associated with overtreatment of asthma with high-dose inhaled corticosteroids (ICS) and poor asthma control, with up to 10% of patients experiencing severe exacerbations, impairment of lung function and quality of life (QoL), and associated healthcare costs [5–7], despite receiving high doses of oral corticosteroids (OCS) [8, 9].

Comprising four component characteristics, including bronchoconstriction, airway inflammation, airway hyperresponsiveness and chronic remodelling of airways, our understanding of the inflammatory mechanisms and immune cell interplay on these components is essential for the development of future treatments for type 2 asthma and comorbidities. Given their frequency, this article focuses on the burden, underlying pathophysiology and management of type 2 inflammation associated with upper and lower airway diseases.

### Epidemiology

Asthma is a complex disease caused by both environmental and genetic factors, and is characterised by chronic wheezing and airflow obstruction, which occurs because of inflammation in the airways of the lungs [10]. Triggered by contact with an allergen, atopic asthma is the most common form of asthma, affecting 70–90% of children and ~50% of adult patients with asthma [11]. The prevalence of atopic diseases is increasing, with allergic asthma, along with atopic dermatitis and allergic rhinitis being described as the milestones of an “atopic march” [12]. Chronic inflammatory airway diseases such as asthma, CRSwNP, COPD with type 2 inflammation, and allergic rhinitis, are prevalent and represent a serious global health concern, creating a substantial clinical and economic burden [13].

Asthma affects 339 million people worldwide [14] and, in 2016, resulted in ~420 000 deaths [15]. The prevalence of CRSwNP, measured using a patient questionnaire, is estimated at ~1.1–4.3%, and increases with age [16]. Approximately 15–37% of patients with COPD have persistent blood eosinophils >2%, which may indicate presence of type 2 inflammation [17, 18]. The prevalence of allergic rhinitis varies widely, from 1.6% to 54% across the world [19]. These patients often have evidence of type 2 inflammation, affecting up to 51% of patients with uncontrolled asthma, 55–70% of patients with severe asthma [20–22], 80% of patients with CRSwNP [23, 24], 49% of patients with CRSsNP [25], 15–37% of patients with COPD [17] and 100% of patients with allergic rhinitis (table 1) [19]. Accordingly, type 2 inflammation is responsible of a number of airway diseases that often coexist together.

Type 2 inflammatory airway diseases are common and represent a substantial clinical burden, with debilitating symptoms, reduced QoL and work productivity [44–47]. The frequent systemic corticosteroid use can lead to increased risk of related adverse effects [26, 48, 49], as well as the substantial burden of comorbid type 2 inflammatory diseases [47, 50–53].

### Burden of disease

#### Asthma

Despite access to ICS and long-acting  $\beta$ -agonist (LABA) combination therapy, patients with uncontrolled asthma frequently suffer from poorly controlled comorbidities as well. These patients have impaired lung function, associated with higher risk of asthma exacerbations, further worsening of their type 2 comorbidities. Asthma and severe CRSwNP are frequently associated with other coexisting type 2 inflammatory diseases such as nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), aspirin-exacerbated respiratory disease (AERD), allergic rhinitis, eosinophilic oesophagitis, atopic dermatitis and type 2 eosinophilic COPD [26–29].

Poorly controlled asthma symptoms in patients treated with prescription medicines are common, and affect between 40% and 54% of adults with asthma in the United States [5, 54]. Patients with poorly controlled asthma have significantly reduced health-related QoL, greater overall work impairment and higher healthcare resource utilisation than those with well-controlled asthma [5, 54, 55]. Moreover, patients with very poorly controlled asthma have been shown to incur more than twice the indirect costs and one and a half times the direct healthcare costs compared with those incurred for well-controlled patients [5]. Patients with well-controlled asthma have been reported to have better physical and mental health; fewer emergency room visits, hospitalisation days and medical provider visits; and lower levels of overall work productivity loss and activity impairment [55]. Although the cost of treating asthma is significant, with an estimated USD 18 billion being spent in the United States alone, about half of patients with asthma continue to be poorly controlled with ICS and LABA treatments [5]. Asthma exacerbations are associated with significant

TABLE 1 Airway diseases driven by type 2 inflammation [17–24, 26–41]

	Evidence of type 2 inflammation	Proportion of type 2 patients	Comorbid disease prevalence
<b>Asthma</b>			
Uncontrolled asthma despite medium- to high-dose ICS	Elevated serum IgE Elevated serum eosinophils	51%	+ CRSwNP 30–50% + Allergic rhinitis >80% + COPD [33] ~13% + NSAID-ERD/AERD ~7%
Severe asthma	Elevated sputum eosinophils Expression of IL-13-inducible genes and Th2 genes in sputum cells	55–70%	
Difficult asthma despite high-dose ICS	Elevated blood eosinophils or $F_{eNO}$	71%	
CRSwNP	Elevated CLC and IL-13 gene expression Elevated IL-5 and Th2 gene expression	~80%	+ Asthma 50% + Allergic rhinitis ~75% + NSAID-ERD/AERD ~10–20%
COPD	Persistent blood eosinophils $\geq 300$ cells· $\mu\text{L}^{-1}$ or $\geq 2\%$	15–37%	A subset may also present with asthma [33] + Allergic rhinitis ~7% + CRS [42, 43]
Allergic rhinitis	IgE-mediated disease driven by type 2 inflammation [10, 37, 38]	100%	Comorbid asthma [37] 19–38% Comorbid CRS [38] ~67%

ICS: inhaled corticosteroids; CRSwNP: chronic rhinosinusitis with nasal polyps; NSAID-ERD: nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; AERD: aspirin-exacerbated respiratory disease; IL: interleukin; Th2: type 2 T-helper;  $F_{eNO}$ : exhaled nitric oxide fraction; CLC: Charcot-Leyden crystals; CRS: chronic rhinosinusitis.

morbidities and account for a substantial proportion of asthma-related costs. Therefore, effective management of asthma and related comorbidities, prevention of subsequent asthma exacerbations and reduction of asthma severity are important to ensure reduction of healthcare costs as well as improvement in the QoL of patients with asthma [56, 57].

Extrapulmonary comorbidities contribute substantially to poor asthma control and a heightened disease burden. Guidelines state that patients with poorly controlled asthma should have a diagnosis confirmed, together with addressing comorbidities before phenotyping the pattern of inflammation [58]. Frequent asthma exacerbations are significantly associated with severe nasal sinusitis, chronic rhinosinusitis, psychological dysfunction, bronchiectasis, gastro-oesophageal reflux, obstructive sleep apnoea, vocal cord dysfunction, obesity, dysfunctional breathing and anxiety/depression [57, 59–65].

#### Allergic rhinitis and chronic rhinosinusitis/CRSwNP

Allergic rhinitis and chronic rhinosinusitis are characterised by inflammation and irritation in the nasal cavities following allergen exposure and are common in patients with asthma, affecting 55–60% and 22–45% of patients, respectively [30, 59, 63, 66, 67]. Indeed, computed tomography has shown that sinusitis may be present in 84% of patients with asthma [68]. Likewise, the increased prevalence of nasal polyps has been associated with asthma severity [69].

Chronic rhinosinusitis is a substantially heterogeneous disease, with patients commonly divided into two subgroups, those with nasal polyps (CRSwNP) and those without nasal polyps (CRSsNP). Although both forms of disease are driven by different inflammatory mechanisms [70, 71], many CRSsNPs can be eosinophilic or have high type 2 inflammation [16]. Patients with CRSwNP are particularly prone to developing asthma, with incidence up to 70%, depending on the degree of type 2 inflammation [72]. Patients with chronic rhinosinusitis have inflammation of the sinonasal mucosa, which results in nasal obstruction, facial pressure or pain, loss of smell and poor drainage lasting for >12 weeks. The surgical and medical management of chronic rhinosinusitis represents a large cost burden, and nasal polyp growth is present in 1–4% of the population of the United States [2, 70]. Notably, patients with CRSwNP may suffer from this condition for decades [72, 73]. In Europe and the United States, the majority of patients with CRSwNP have significant eosinophilic infiltration and elevated levels of IgE in their nasal polyp tissue [2]. Likewise, higher levels of eosinophils in the serum and sputum in these conditions suggest a close relationship between asthma and chronic rhinosinusitis [68].

### *Asthma and associated type 2 inflammatory airway diseases*

Type 2 inflammatory airway diseases, such as asthma, CRSwNP, NSAID-ERD/AERD, eosinophilic COPD and allergic rhinitis often coexist in the same patient, and are driven by a similar underlying type 2 pathophysiology [31]. The risk of asthma symptoms increases with increasing presence of CRSwNP [74] along with the increased likelihood of poor asthma control [75, 76]. Likewise, the presence of a comorbid type 2 inflammatory disease increases the severity and clinical burden of CRSwNP, with disease severity being significantly greater in patients with CRSwNP and asthma *versus* those with CRSwNP alone [53]. The presence of a comorbid type 2 inflammatory disease has also been associated with an increased risk of recurrence of nasal polyps post-surgery in patients with CRSwNP [77].

The coexistence of type 2 inflammatory diseases is associated with greater decline in lung function and clinical outcomes in patients with asthma. A 5-year study of patients with recently diagnosed adult-onset asthma showed that the presence of comorbid nasal polyps was significantly associated with a greater decline in post-bronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>) per year [78]. Moreover, comorbid disease has been shown to increase disease burden in patients whose asthma is driven by type 2 inflammation, with the presence of rhinitis, nasal polyps or atopic dermatitis as independent predictors for future asthma exacerbations [79].

Both persistent uncontrolled asthma and CRSwNP contribute to the burden of disease and are common causes of sleep disturbance and fatigue. These conditions have been shown to lead to decreased daytime functioning and reduced QoL [45, 80], as well as having negative impacts on both physical and mental health [47, 81–83]. The impact of these diseases on work productivity and absenteeism has also been shown to result in substantial indirect costs. Almost half of CRSwNP patients awaiting surgery experiencing reduced productivity and a 40–60% overall work impairment in asthma patients despite receiving LABA or ICS treatment. Similarly, a study of >8000 asthma patients with comorbid COPD showed a significantly increased likelihood of severe exacerbations of asthma and COPD, *versus* healthy nonsmoker controls, with greater annual decline in FEV<sub>1</sub> *versus* asthma or COPD alone [84].

Severe uncontrolled asthma or acute episodes of CRSwNP are frequently treated with OCS. However, this can contribute to the short- and long-term burden of disease. Short-term effects include mood and sleep disturbances, while long-term consequences include osteoporosis, gastrointestinal bleeds, type 2 diabetes, obesity, cataracts and glaucoma [1, 85]. All these conditions have been shown to contribute significantly to patients' health concerns [86]. Moreover, the healthcare cost of OCS-related side-effects is substantial. Asthma patients with comorbid disease while on OCS generate twice as much healthcare cost compared with nonasthmatic patients [87]. Similarly, patients with CRSwNP taking OCS have higher total healthcare costs compared with those not taking OCS [88]. A systematic literature review over three decades of research has also shown a higher clinical and economic burden in patients with allergic rhinitis and asthma results, with a 1.2- to 2.1-fold increase in annual costs for these patients [89]. Similar results from a United States-based study showed substantially greater healthcare utilisation among patients with both asthma and COPD *versus* those with asthma or COPD alone, with medical service costs being five times greater in this group than in patients with asthma alone [89].

### Type 2 inflammation: pathophysiology

Type 2 inflammation is driven by both the adaptive and innate arms of the immune system and underpins the pathophysiology of several chronic upper and lower airway diseases, including asthma, COPD, CRSwNP and allergic rhinitis [90–92]. Type 2 inflammation is driven by Th2 cells and group 2 innate lymphoid cells (ILC2), which produce the type 2 cytokines, including interleukin (IL)-4, IL-5 and IL-13, as well as other inflammatory mediators (tables 2 and 3) [31, 100–102]. Type 2 cytokines have a range of roles in the pathophysiology of type 2 inflammatory airway diseases. IL-5 plays a pivotal role in the differentiation and maturation of IL-5R $\alpha$ <sup>+</sup> eosinophil progenitors in the bone marrow, as well as their mobilisation and survival. In addition, IL-5 supports the development of other type 2 cells, including mast cells and basophils [103]. IL-4 and IL-13 both play a role in B-cell class switching and IgE production, leading to the degranulation of basophils and mast cells and subsequent release of pro-inflammatory mediators as well as barrier disruption and tissue remodelling [31, 91]. IL-13 is involved in goblet-cell hyperplasia and mucus production [31, 91], as well as smooth muscle contractility and hyperplasia [104]. Moreover, IL-13-mediated damage to the epithelial barriers is also associated with the development of mucus plugs as a consequence of mucus production [104].

IL-4, IL-13 and IL-5 are all involved in trafficking of eosinophils to tissues (figure 1) [3, 31, 105–107]. These common pathophysiological effects, driven by type 2 inflammation, manifest as clinical symptoms, including nasal polyps, loss of smell, and nasal obstruction in CRSwNP [3], and impaired lung function,

**TABLE 2** Central drivers of type 2 inflammation interleukin (IL)-4 and IL-13 have unique and overlapping functions, contributing the pathophysiology of asthma, chronic rhinosinusitis with nasal polyps and allergic rhinitis [3, 31, 92, 93, 93–99]

IL-4	IL-13	IL-5
Th2 cell differentiation	Goblet cell hyperplasia Mucociliary dysfunction Excess mucus production	Eosinophil differentiation and survival
	Collagen deposition Smooth muscle proliferation	
	Increased contractility Hyperresponsiveness	
	Neuroimmune dysfunction	
	B-cell isotype switching and IgE production; mast cell and basophil degranulation	
	Mast cell activation and trafficking to tissue Fibrosis and airway remodelling	
	Epithelial barrier dysfunction and microbiome imbalance	
	TARC-induced migration of Th2 cells	
	Activation of macrophages to M2 type Eosinophil recruitment and trafficking to tissue	

Th2: type 2 T-helper; TARC: thymus and activation-regulated chemokine.

wheezing, shortness of breath, chest tightness and coughing in asthma [1]. The key and central cytokines for type 2 airway diseases include IL-4 and IL-13. IL-4 upregulates differentiation of naive Th0 cells into Th2 cells, which produce IL-4, IL-13 and IL-5, thus creating a cyclical effect [31]. IL-4, IL-5 and IL-13 also induce chemokines (*i.e.* eotaxin-3, thymus- and activation-regulated chemokine) and vascular cell adhesion molecule 1, which promote migration and trafficking of inflammatory cells, including eosinophils, to the site of inflammation [3, 31]. Eosinophils are activated by IL-5 and are recruited to the airway directly or indirectly by IL-4, IL-13 and IL-5 [31].

**Type 2 inflammation in asthma**

More specific to asthma, IL-13 has effects on goblet and airway smooth muscle cells, which impact mucus secretion, smooth muscle contractility and basement membrane thickening [31]. Moreover, in asthma, along with the production of mucus, IL-13 facilitates airway obstruction by tethering to mucus-producing cells in the epithelium and impairing mucociliary transport, identified by the expression of the mucin 5AC (MUC5AC) protein, which is considered to be a marker of airway goblet cells and mucus hypersecretion [108], leading to the development of mucosal plugs. Nitric oxide production is also upregulated by IL-13 in asthma [109].

**Type 2 inflammation in nasal polyposis**

In patients with CRSwNP, an increased inflammatory response results from an innate immune function, causing defects in the nasal epithelial barrier, with subsequent reduced secretion of innate host defence

**TABLE 3** Pathophysiological features of type 2 inflammatory airway diseases [3, 31, 92–99]

Asthma (IL-4, IL-13, IL-5)	CRSwNP (IL-4, IL-13, IL-5)	Allergic rhinitis (IL-4, IL-13, IL-5)
Inflammatory cell trafficking to the tissue IgE production Goblet cell hyperplasia/mucus production Barrier dysfunction Tissue remodelling Smooth muscle proliferation/contractility	Inflammatory cell trafficking to the tissue IgE production Goblet cell hyperplasia/mucus production Barrier dysfunction Tissue remodelling Microbiome alterations	Inflammatory cell trafficking to the tissue IgE production Goblet cell hyperplasia/mucus production Barrier dysfunction

IL: interleukin; CRSwNP: chronic rhinosinusitis with nasal polyps.



Goblet-cell hyperplasia, excess mucus production and mucociliary dysfunction are also features of type 2 inflammatory remodelling in both asthma and CRSwNP [104, 111–113].

In CRSwNP, IL-4 and IL-13 induce activation of M2-type macrophages, which contribute to the pathogenesis of CRSwNP by inducing fibrin deposition, oedematous remodelling and polyp formation, while IL-13 has additional effects on goblet cells, mucus production and nasal epithelial cell mucociliary differentiation [3, 114]. Likewise, in patients with upper airway disease such as CRSwNP, IL-13 supports alterations in nasal epithelium, inducing MUC5AC, in turn impairing ciliary function [115].

As mentioned, IL-4 and IL-13 are key and central type 2 cytokines in type 2 inflammation and have an important role to play in driving airway and tissue remodelling in type 2 inflammatory diseases of the upper and lower airways [3, 31, 91, 116–118]. Airway wall thickening in both asthma and CRSwNP is driven by overexpression of both IL-4 and IL-13, inducing fibrosis through transforming growth factor- $\beta$  [119]. Type 2 inflammation is also key to the remodelling processes involved in polyp formation, with IL-4 and IL-13 causing a decrease in tight junction proteins and activation of epithelial-to-mesenchymal transition induction [3] and membrane thickening. Additionally, IL-4 and IL-13 contribute to remodelling and nasal polyp formation in CRSwNP by inducing activation of macrophages to M2 macrophages and inhibiting fibrin degradation (IL-13) [3, 114].

#### *Type 2 inflammation in allergic rhinitis*

The pathophysiology of allergic rhinitis is similar to that of other upper inflammatory airway diseases, such as CRSwNP. Type 2 inflammatory cells and mediators, including Th2 cells and ILC2, drive the type 2 response cascade leading to the release of further response mediators, including the interleukins IL-4, IL-13 and IL-5, and eosinophils [31]. As with CRSwNP, these type 2 inflammatory drivers result in goblet-cell hyperplasia, mucus production and barrier dysfunction. The role of IgE in allergic rhinitis is very important: on allergen contact, cross-linking IgE bound to its receptor induces mast cells to release granules and subsequently chemical mediators, resulting in inflammation [120–122].

#### *Other comorbidities*

Type 2 inflammation underpins multiple other comorbid diseases including atopic dermatitis, allergic bronchopulmonary aspergillosis [123], AERD, ocular diseases, eosinophilic oesophagitis and other gastrointestinal disorders, and food allergies.

Elevated IgE levels are common in patients with atopic dermatitis who have history of allergic rhinitis and asthma [124] and up to one-third of children with atopic dermatitis develop asthma [125]. Moreover, both IL-4 and IL-13 play key roles in modulation of the epidermal barrier and development of atopic dermatitis, with many children having higher levels of serum IL-13 than healthy children [126].

Allergic bronchopulmonary aspergillosis, sometimes classified as a subtype of asthma, affects approximately 5 million patients with asthma, representing an 8.4% comorbidity [123]. It is an IgE-mediated disease, with increased IgE and IgG antibodies and peripheral blood eosinophilia [6], resulting in chronic mucus hypersecretion and accelerated loss of lung function [127]. As in AERD, both upper airway pathology and lower airway pathology in NSAID-ERD patients are characterised by chronic and extensive eosinophilic mucosal inflammation related to abnormalities of both cyclo-oxygenase- and lipoxygenase-derived arachidonic acid metabolism [128]. Food allergy (*e.g.* eggs) could also be associated with asthma, especially in early life [129]. The predisposition for asthma in patients with food allergies is clear and should not be ignored, with preventable interactions manifesting in the form of respiratory symptoms and bronchial hyperreactivity during food-induced anaphylaxis, and severe asthma resulting from the cross-reactivity between pollen and allergens from fruits and vegetables [130].

#### *Biomarkers for type 2 inflammation*

The heterogeneous nature of asthma and its comorbidities requires identification of biomarkers and timely introduction of early and effective personalised medicine for those not being adequately managed by ICS and LABA alone. Inflammatory cytokines (IL-4, IL-13 and IL-5) and their receptors, among others, are important targets for treating type 2 asthma, since they promote an increase in inflammation. Fractional exhaled nitric oxide ( $F_{eNO}$ ), thymus and activation-regulated chemokine (TARC), eotaxin, periostin, IgE and blood eosinophil counts have all emerged as predominant biomarkers for type 2 inflammatory airway diseases, providing opportunities for better disease targeting, improving patients' health-related QoL, and reducing direct and indirect cost burdens associated with ineffective management of asthma in the long term.  $F_{eNO}$  and blood eosinophil count are produced through the action of cytokine mediators [31, 100–102, 131–134]. Chemotactic biomarkers of type 2 inflammation include eotaxin-3 and TARC, which are

chemoattractants stimulated by IL-4 and IL-13; however, no single biomarker pathway is solely responsible for type 2 inflammation in airway diseases.

Recent asthma guidelines recommend the use of type 2 biomarkers to establish the cause of asthma and determine the best course of treatment [1]. The Global Initiative for Asthma (GINA) [1] defines type 2 airway inflammation when the following criteria are met: blood eosinophils  $\geq 150$  cells· $\mu\text{L}^{-1}$  and/or  $F_{\text{eNO}} \geq 20$  ppb and/or sputum eosinophils  $\geq 2\%$  and/or asthma clinically allergen-driven and/or need for maintenance OCS (repeat blood eosinophils and  $F_{\text{eNO}}$  up to three times, on lowest possible OCS dose) [1]. However, despite candidate biomarkers being identified, there are no recommendations as yet for testing in CRSwNP. Endotyping, phenotyping, treatment response and biomarkers are a rapidly evolving fields and further research is needed [2].

## Management of severe asthma and other airway diseases with type 2 inflammation

### Guidelines

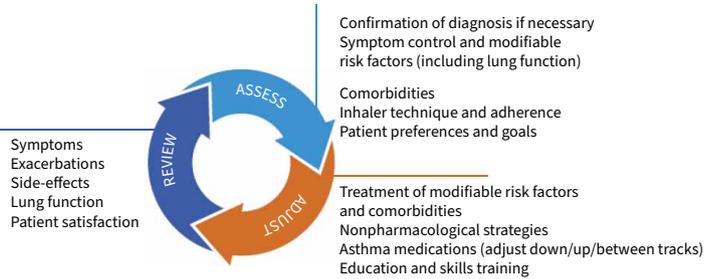
The goals of asthma management include achieving control of symptoms and maintaining normal activity levels for physical and social development, while minimising the risk of disease exacerbation, impaired lung development, and side-effects associated with medications [1, 85, 86]. The GINA 2021 guidelines' stepwise approach to the management of asthma (figure 2) [1] ranges from steps 1 and 2 with as-needed reliever medications (low-dose ICS-formoterol as a preferred option or a short-acting  $\beta$ -agonist as an alternative) and low-dose ICS as a controller, through steps 3 and 4 treatment with low- to medium-dose maintenance of ICS-formoterol or ICS/LABA, to step 5 with a high dose of dual controllers or the addition of a third controller with long-acting muscarinic antagonists and biological therapies. Low-dose OCS could be an alternative, but side-effects should be considered. Despite these comprehensive guidelines, the management of moderate and severe forms of atopic diseases such as asthma remain a challenge for physicians. It is apparent that comorbidities are important in the management of severe asthma, as they may contribute to poor disease control by both exacerbating and mimicking symptoms of asthma, resulting in overtreatment of asthma symptoms and increased costs. Given the heterogeneous pathobiology and multiple phenotypes of asthma and its associated comorbidities, there is a need for a personalised approach for the diagnosis and subsequent management of asthma. Type 2 inflammation underlies type 2 asthma and associated comorbidities, and there is a need to fully understand allergic, eosinophilic and combined phenotypes to ensure improvements in the management of this disease. Nevertheless, the key treatment objective for all patients with asthma includes full control of the disease with minimum side-effects.

Current guidelines, including those from GINA (2021) [1], the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) (2020) [2] and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) (2019) [16] recognise that side-effects associated with standard of care (*i.e.* standard care services) should be minimised, while acknowledging the major role of type 2 inflammation in asthma and CRSwNP, as well as other inflammatory airway diseases. The GINA guidelines [1] recommend considering add-on type-2-targeted biological treatments for patients with exacerbations or poor symptom control on high-dose ICS+LABA, and who have allergic or eosinophilic biomarkers, or need maintenance OCS. These guidelines include the use of either an anti-IL-4 receptor as add-on treatment, anti-IgE or anti-IL-5 in patients with severe asthma who do not adequately respond to the standard of care. Anti-IL-4R $\alpha$  agents block the signalling of both IL-4 and IL-13 [135]. The EPOS guidelines [2] also highlight the role of type 2 inflammation in CRSwNP and the impact of comorbid diseases on CRSwNP, highlighting the need to take these diseases into consideration when treating CRSwNP. Likewise, the EUFOREA [16] guidelines recommend development of a multidisciplinary integrated care pathway in daily practice where all patients with chronic rhinosinusitis receive at least one systematic assessment for asthma and allergic rhinitis, ideally using a validated questionnaire along with systematic evaluation of their upper and lower airways at every clinical visit.

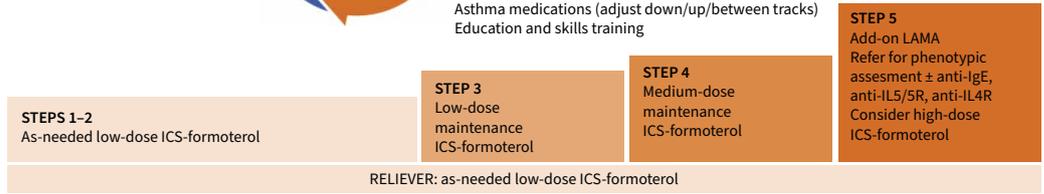
### Standard of care and unmet needs

The majority of type 2 inflammatory airway diseases, such as asthma and CRSwNP, remain poorly controlled with the current standard of care [48, 136]. A substantial proportion (23–32%) of asthma patients treated with ICS and LABA have been shown not to achieve GINA-defined well-controlled asthma after 1 year of ICS $\pm$ LABA use [137]. Similarly, although surgical removal of nasal polyps is the standard of care in patients with severe CRSwNP, following oral or systemic corticosteroid treatment, 80% of these patients experience recurrence of polyps. The overuse of systemic corticosteroids is associated with adverse effects, including immunosuppression, weight gain, diabetes, osteoporosis, glaucoma, anxiety and depression and cardiovascular disease [138, 139].

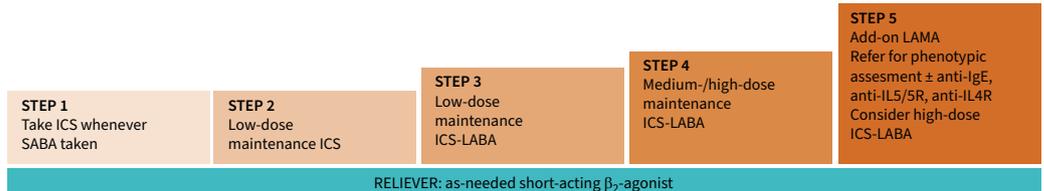
**Adults and adolescents**  
 >12 years  
 Personalised asthma management  
 Assess, adjust, review  
 for individual patient needs



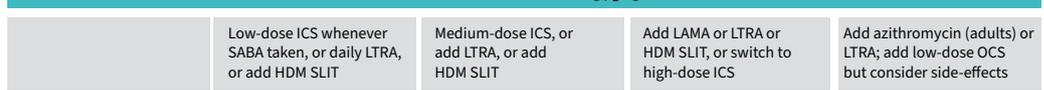
**CONTROLLER and PREFERRED RELIEVER**  
 (track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever



**CONTROLLER and ALTERNATIVE RELIEVER**  
 (track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller



Other controller options for either track



**Assess and treat severe asthma phenotypes**

Continue to optimise management (including inhaler technique, adherence, comorbidities)



**Assess the severe asthma phenotype during high-dose ICS treatment (or lowest possible dose of OCS)**

**Type 2 inflammation**

**Could patient have Type 2 airway inflammation?**

- Blood eosinophils ≥150 cells·μL<sup>-1</sup> and/or
- F<sub>ENO</sub> ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven and/or
- Need for maintenance OCS

Note: these are not the criteria for add-on biologic therapy (see 6b)

(Repeat blood eosinophils and F<sub>ENO</sub> up to 3x, on lowest possible OCS dose)

**Investigate for comorbidities/differential diagnoses and treat/refer as appropriate**

- Consider: CBC, CRP, IgG, IgA, IgE, fungal precipitins; chest radiography and/or HRCT chest; D<sub>LCO</sub>
- Skin prick testing or specific IgE for relevant allergens, if not already done
- Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enrol in registry (if available) or clinical trial (if appropriate)

Consider add-on type 2-targeted biologic for patients with exacerbations or poor symptom control on high-dose ICS-LABA, who:

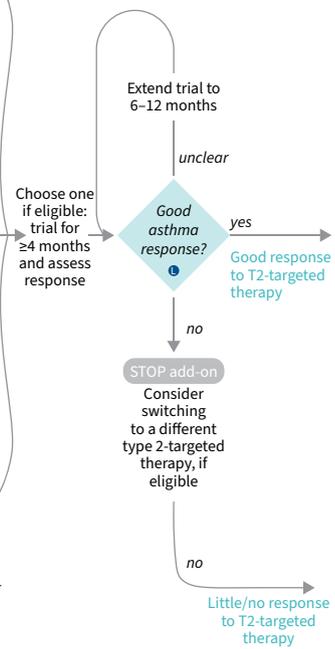
- have eosinophilic or allergic biomarkers, or
- need maintenance OCS

Consider local payer eligibility criteria, comorbidities and predictors of response when choosing between available therapies

Also consider cost, dosing frequency, route (s.c. or i.v.) patient preference

Which biologic is appropriate to start first?

<b>Anti-IgE</b>	<b>Anti-IL5/ Anti-IL5R</b>	<b>Anti-IL4R</b>
Is the patient eligible for anti-IgE for severe allergic asthma?	Is the patient eligible for anti-IL5/anti-IL5R for severe eosinophilic asthma?	Is the patient eligible for anti-IL4R ... for severe eosinophilic/type 2 asthma?
<ul style="list-style-type: none"> <li>Sensitisation on skin prick testing or specific IgE</li> <li>Total serum IgE and weight within dosage range</li> <li>Exacerbations in last year</li> </ul>	<ul style="list-style-type: none"> <li>Exacerbations in last year</li> <li>Blood eosinophils, e.g. 150 cells·μL<sup>-1</sup> or 300 cells·μL<sup>-1</sup></li> </ul>	<ul style="list-style-type: none"> <li>Exacerbations in last year</li> <li>Blood eosinophils ≥150 cells·μL<sup>-1</sup> or F<sub>ENO</sub> ≥25 ppb</li> </ul>
<ul style="list-style-type: none"> <li>Blood eosinophils ≥260 cells·μL<sup>-1</sup>++</li> <li>F<sub>ENO</sub> ≥20ppb+</li> <li>Allergen-driven symptoms+</li> <li>Childhood-onset asthma+</li> </ul>	<ul style="list-style-type: none"> <li>Higher blood eosinophils+++</li> <li>More exacerbations in previous year+++</li> <li>Adult-onset asthma++</li> <li>Nasal polyposis++</li> </ul>	<ul style="list-style-type: none"> <li>Higher blood eosinophils+++</li> <li>Higher F<sub>ENO</sub>+++</li> </ul>
What factors may predict good asthma response to anti-IgE?	What factors may predict good asthma response to anti-IL5/5R?	What factors may predict good asthma response to anti-IL4R?



Eligible for none?  
 Return to section 6a

Check local eligibility criteria for specific biologic therapies as these may vary from those listed

**FIGURE 2** The Global Initiative for Asthma stepwise approach to control symptoms and minimise future asthma risk in adults and adolescents aged >12 years [1]. ICS: inhaled corticosteroid; SABA: short-acting  $\beta$ -agonist; LAMA: long-acting muscarinic antagonist; IL: interleukin; LABA: long-acting  $\beta$ -agonist; LTRA: leukotriene receptor antagonist; HDM: house dust mite; SLIT: sublingual allergen immunotherapy; OCS: oral corticosteroid;  $F_{eNO}$ : exhaled nitric oxide fraction; *s.c.*: subcutaneous; *i.v.*: intravenous; CBC: complete blood count; CRP: C-reactive protein; HRCT: high-resolution computed tomography;  $D_{LCO}$ : diffusing capacity of the lung for carbon monoxide; ANCA: antineutrophil cytoplasmic antibodies; CT: computed tomography; BNP: brain natriuretic peptide.

Standard of care treatments have nonspecific anti-inflammatory effects on a range of cell types, often targeting symptoms, but do not specifically target cytokines (IL-4, IL-13 and IL-5) involved in inflammation, and can lead to serious treatment-related adverse effects and costs [1, 2, 140]. This unmet need has led to the development of cytokine-targeted therapies and the biological-focused management of type 2 inflammatory airway diseases. Although IL-13 can be inhibited by ICS, there is a proportion of uncontrolled asthma patients who, despite treatment with high-dosage ICS and systemic corticosteroids, have elevated levels of IL-13 in their sputum [141]. Hence, the IL-13 pathway has been identified as a potential therapeutic target in severe asthma and associated allergic diseases, with selective monoclonal antibody therapies being developed. There is a clear need for unified management of these type 2 inflammatory airway diseases.

### Targeted therapies

Improved understanding of the type 2 inflammatory mediators described here has led to the development of targeted therapies for upper and lower type 2 inflammatory airway diseases, many of which are yielding promising results in difficult-to-treat asthma patients. The six biological therapies approved for asthma so far, and some other type 2 inflammatory diseases, include omalizumab (anti-IgE), mepolizumab (anti-IL-5), reslizumab (anti-IL-5), benralizumab (anti-IL-5R $\alpha$ ), dupilumab (anti-IL-4R $\alpha$ ) and tezepelumab (anti-thymic stromal lymphopoietin (TSLP)), each of these targeting specific cytokines involved in the type 2 inflammatory cascade (table 4). Omalizumab is approved as an add-on treatment for moderate-to-severe persistent allergic asthma inadequately controlled with ICS and for severe CRSwNP. Omalizumab binds to free circulating IgE [145, 146]; however, because IgE production occurs downstream of Th2 cell activation and IL-4 and IL-13 release, it can only target one feature of the type 2 inflammatory response [147–152]. Three anti-IL-5 therapies (mepolizumab, reslizumab and benralizumab) are approved as add-on agents for the treatment of severe eosinophilic asthma [143, 153–157]. Mepolizumab and reslizumab inhibit IL-5 activity by blocking the binding of IL-5 to the receptor expressed on the eosinophils cell surface, while benralizumab binds directly to IL-5R $\alpha$  expressed on eosinophils and basophils. Dupilumab is a human monoclonal antibody, which binds specifically to the shared receptor component for IL-4 and IL-13, thus inhibiting the dual signalling pathways of both IL-4 and IL-13 [31]. Thus, dupilumab inhibits IL-4 signalling *via* the type 1 receptor and both IL-4 and IL-13 signalling through the type 2 receptor.

Each of these targeted biological agents have demonstrated clinical benefits in patients with type 2 inflammatory airway diseases. Two of three pivotal trials of omalizumab, as an add-on to high-dose ICS plus LABA, demonstrated reduced asthma exacerbations in adolescents and adults with moderate-to-severe asthma with an allergic phenotype [145]. However, omalizumab may have limited effects on lung function. Similar results were seen in two trials of mepolizumab in patients selected with raised blood eosinophil levels (Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) and Steroid Reduction with Mepolizumab Study (SIRIUS)), which, despite not showing consistent improvement in lung function across trials, significantly reduced asthma exacerbations as well as improving QoL [158]. However, anti-IL-5 treatment was successful in the MENSA and SIRIUS trials in patients selected for raised blood eosinophil levels. Intravenous reslizumab has also demonstrated significant improvements in lung function, asthma exacerbations [159, 160] and QoL; however, reduction in OCS daily dose was not achieved with the subcutaneous formulation [159, 161]. Similar results were seen in the CALIMA and SIROCCO trials of benralizumab, with beneficial effects on exacerbations, lung function and QoL; however, these benefits were only seen consistently in patients with blood eosinophil count  $\geq 300$  cells· $\mu\text{L}^{-1}$  [162]. A recent study found a significant reduction in exacerbations and reduced need for OCS in patients following 1 year of treatment with benralizumab [163]. Clinical trials of dupilumab demonstrate reduced asthma exacerbations and produced rapid and sustained improvements in lung function, QoL and asthma control in patients with uncontrolled persistent asthma [164–167]. Moreover, dupilumab has enabled reduction in OCS use, regardless of type 2 inflammatory biomarker at baseline, while maintaining reductions in exacerbations and improvements in lung function, QoL and asthma control in a broad population of adults with severe steroid-dependent asthma [168].

TABLE 4 Approved biological therapies for type 2 inflammatory airway diseases

	Omalizumab (anti-IgE)	Mepolizumab (anti-IL-5)	Reslizumab (anti-IL-5)	Benralizumab (anti-IL-5R)	Dupilumab (anti-IL-4R)	Tezepelumab (anti-TSLP)
<b>Approval (asthma)</b>	US indication: patients with moderate-to-severe persistent allergic asthma aged $\geq 6$ years EMA indication: patients with severe persistent allergic asthma aged $\geq 6$ years	US indication: patients with severe eosinophilic asthma aged $\geq 6$ years EMA indication: patients with severe refractory eosinophilic asthma aged $\geq 6$ years	US indication: patients with severe eosinophilic asthma aged $\geq 18$ years EMA indication: patients with severe refractory eosinophilic asthma aged $\geq 18$ years	US indication: patients with severe eosinophilic asthma aged $\geq 12$ years EMA indication: patients with severe refractory eosinophilic asthma aged $\geq 18$ years	US indication: patients with moderate-to-severe eosinophilic asthma or OCS-dependent asthma aged $\geq 6$ years [142] EMA indication: patients with severe asthma with type 2 inflammation (elevated $F_{eNO}$ /eosinophils) aged $\geq 12$ years	US indication: patients with severe asthma aged $\geq 12$ years
<b>Approval (CRSwNP)</b>	Approved EU and US CRSwNP inadequately controlled	EMA indication: inadequately controlled severe CRSwNP US indication: inadequately controlled CRSwNP [143]	Phase 3 recruiting CRS with elevated eosinophils	Phase 3 complete severe symptomatic bilateral nasal polyps	Approved EU and US CRSwNP inadequately controlled	Phase 3 recruiting
<b>Approval (COPD)</b>	Phase 2 withdrawn Lack of eligible COPD subjects with elevated IgE	Phase 3 complete COPD with elevated eosinophil count		Phase 3 complete COPD with exacerbation history	Phase 3 recruiting Moderate-to-severe COPD with type 2 inflammation	Phase 2a recruiting [144]
<b>Approval (other)</b>	Chronic idiopathic urticaria	Eosinophilic granulomatosis with polyangiitis Hypereosinophilic syndrome			Atopic dermatitis	

IL: interleukin; TSLP: thymic stromal lymphopoietin; CRSwNP: chronic rhinosinusitis with nasal polyps; US: United States; EMA: European Medicines Agency; OCS: oral corticosteroids;  $F_{eNO}$ : exhaled nitric oxide fraction; EU: European Union; CRS: chronic rhinosinusitis.

In patients with comorbid CRSwNP, mepolizumab has reduced the rate of asthma exacerbations [169, 170]. Similar results have been seen with benralizumab in patients with asthma and comorbid CRSwNP [171]. In patients with eosinophilic asthma and self-reported CRSwNP, after 52 weeks' reslizumab add-on therapy, asthma exacerbations were reduced by 83% and lung function (FEV<sub>1</sub>) improved compared with placebo; QoL and Asthma Control Questionnaire score were also reported to have improved in this population of eosinophilic asthma with nasal polyps [172, 173].

There is a comprehensive clinical trials programme of dupilumab in patients with CRSwNP, which has shown that dupilumab provides rapid and continuous improvement in clinical symptoms (*e.g.* nasal congestion, loss of smell and rhinorrhea), QoL, polyp size and sinus disease in patients uncontrolled on standard of care [174]. Moreover, dupilumab has been shown to reduce the need for systemic corticosteroids and/or the need for sinonasal surgery in adults with severe CRSwNP [175]. Furthermore, clinical trials of dupilumab have demonstrated improvements in patients with asthma and comorbid CRSwNP, including exacerbations, lung function, asthma control and QoL [176–178]. In addition, dupilumab has been shown to allow reduction of OCS dose in this patient cohort [179], and in patients presenting with CRSwNP and comorbid asthma [180]. Trials of each of these biologicals have presented a good and consistent safety profile in patients with type 2 inflammatory airway diseases. In conjunction with clinically meaningful improvement in symptoms, lung function and QoL, as well as reduction in corticosteroid use, biologicals represent an important advance in the management of uncontrolled asthma and comorbid type 2 inflammatory airway diseases.

With a better understanding of asthma pathophysiology, upstream targets of type 2 inflammation have been identified such as alarmins (IL-33 or TSLP) and some emerging biological therapies targeting those epithelial-derived cytokines are under investigation with a need for patients with type 2 low or non-type 2 asthma [181]. More recently, tezepelumab, a TSLP blocker, has been approved by the United States Food and Drug Administration as an add-on maintenance treatment in severe asthma [182].

## Conclusions

Effective management of type 2 inflammatory airway diseases represents a major unmet need. Severe asthma continues to outpace asthma control in patients whose disease is managed by LABA and ICS, resulting in significant cost burden and impact on QoL of affected patients. Identifying individuals with comorbidities is important for adequate control of severe type 2 asthma, most notably with novel biological therapies that target the immune biomarkers, such as IL-4, IL-5 and IL-13. A substantial proportion of patients with asthma or severe CRSwNP remain suboptimally controlled with conventional therapies, highlighting the need for new therapies that target disease pathophysiology. Treatment guidelines for the management of asthma and CRSwNP are focused on improving signs and symptoms and achieving disease control. As treatment guidelines continue to acknowledge the value of, and recommend targeted therapies for, the treatment of asthma and comorbid type 2 inflammatory airway diseases, global access to these therapies becomes increasingly important to patients, clinicians, and society. There still remains a need for a unified treatment strategy for patients with coexisting type 2 inflammatory diseases.

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