GLOBAL INITIATIVE FOR ASTHMA®

2026

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

DIAGNOSIS AND MANAGEMENT

A Short GINA Guide for Health Professionals

V7.0 May 2026

Global Initiative for Asthma. P.O. Box 558 Fontana, Wisconsin 53125, USA

First published 2018

V7.0, May 2026

Difficult-to-treat and severe asthma in adolescent and adult patients

DIAGNOSIS AND MANAGEMENT

A Short GINA Guide for Health Professionals

Prepared by the GINA Science Committee from the GINA 2026 Report, which was published on May 5, 2026.
Acknowledgements are on page 35.

Suggested citation: Global Initiative for Asthma. Difficult-To-Treat & Severe Asthma in Adolescent and Adult Patients, V7.0, May 2026. Available from: **www.ginasthma.org/reports**

The reader acknowledges that this report is intended as an evidence-based asthma management strategy, for the use of health professionals and policy-makers. It is based, to the best of our knowledge, on current best evidence and medical knowledge and practice at the date of publication. When assessing and treating patients, health professionals are strongly advised to use their own professional judgment, and to take into account local and national regulations and guidelines. GINA cannot be held liable or responsible for inappropriate health care associated with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.

Abbreviations

ABPA	Allergic bronchopulmonary aspergillosis
ACQ	Asthma Control Questionnaire
AERD	Aspirin-exacerbated respiratory disease
Anti-IL4Rα	Anti-interleukin 4 receptor alpha (monoclonal antibody)
Anti-IL5	Anti-interleukin 5 (monoclonal antibody)
Anti-IL5Rα	Anti-interleukin 5 receptor alpha (monoclonal antibody)
Anti-TSLP	Anti-thymic stromal lymphopoietin (monoclonal antibody)
COVID-19	Coronavirus disease 2019
CT	Computerized tomography
CXR	Chest X-ray
EGPA	Eosinophilic granulomatosis with polyangiitis
FeNO	Fractional concentration of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second (measured by spirometry)
GERD	Gastro-esophageal reflux disease (GORD in some countries)
ICS	Inhaled corticosteroid
Ig	Immunoglobulin
IL	Interleukin
ILO	Inducible laryngeal obstruction
IV	Intravenous
LABA	Long-acting $beta_2$ agonist
LAMA	Long-acting muscarinic antagonist (also called long-acting anticholinergic)
LM	Leukotriene modifier
LTRA	Leukotriene receptor antagonist
MART	Maintenance-and-reliever therapy with ICS-formoterol; in some countries called SMART (single-inhaler maintenance-and-reliever therapy)
NSAID	Nonsteroidal anti-inflammatory drug
OCS	Oral corticosteroids
OSA	Obstructive sleep apnea
QTc	Corrected QT interval on electrocardiogram
RCT	Randomized controlled trial
SABA	Short-acting $beta_2$ agonist
SC	Subcutaneous
T2	Type 2 airway inflammation (an asthma phenotype)
TB	Tuberculosis
TSLP	Thymic stromal lymphopoietin
VCD	Vocal cord dysfunction (included in inducible laryngeal obstruction)

Table of Contents

Figures & Tables

Purpose of this guide

This guide is a practical summary of GINA guidance on how to identify, assess and manage difficult-to-treat and severe asthma in adolescents and adults. It is intended for use by general practitioners (GPs, primary care physicians), pulmonary specialists and other health professionals involved in the care of people with asthma.

Comprehensive guidance on asthma management is provided in the Global Strategy for Asthma Management and Prevention (the Strategy Report), available from **www.ginasthma.org**.

How this guide was developed

This guide is based on the 2026 GINA Strategy Report, published on May 5, 2026.

The recommendations were developed by the GINA Science Committee based on the most reliable sources available:

- Evidence from good-quality systematic reviews or randomized controlled trials (RCTs)
- Robust observational data for topics with no RCTs
- Expert consensus among experienced clinicians and researchers for topics with no published evidence.

The first edition of this guide and decision tree was developed through collaboration with experts in human-centered design. Best-practice information architecture and diagramming principles were employed to translate clinical guidance into effective flowcharts and graphic design, to help users find relevant information easily and apply it in practice.

Acknowledgements are on page 35.

How to use this Guide

The **table of contents** (page 4) summarizes the overall steps involved in assessing and treating an adult or adolescent who presents with difficult-to-treat asthma (see definitions on page 8).

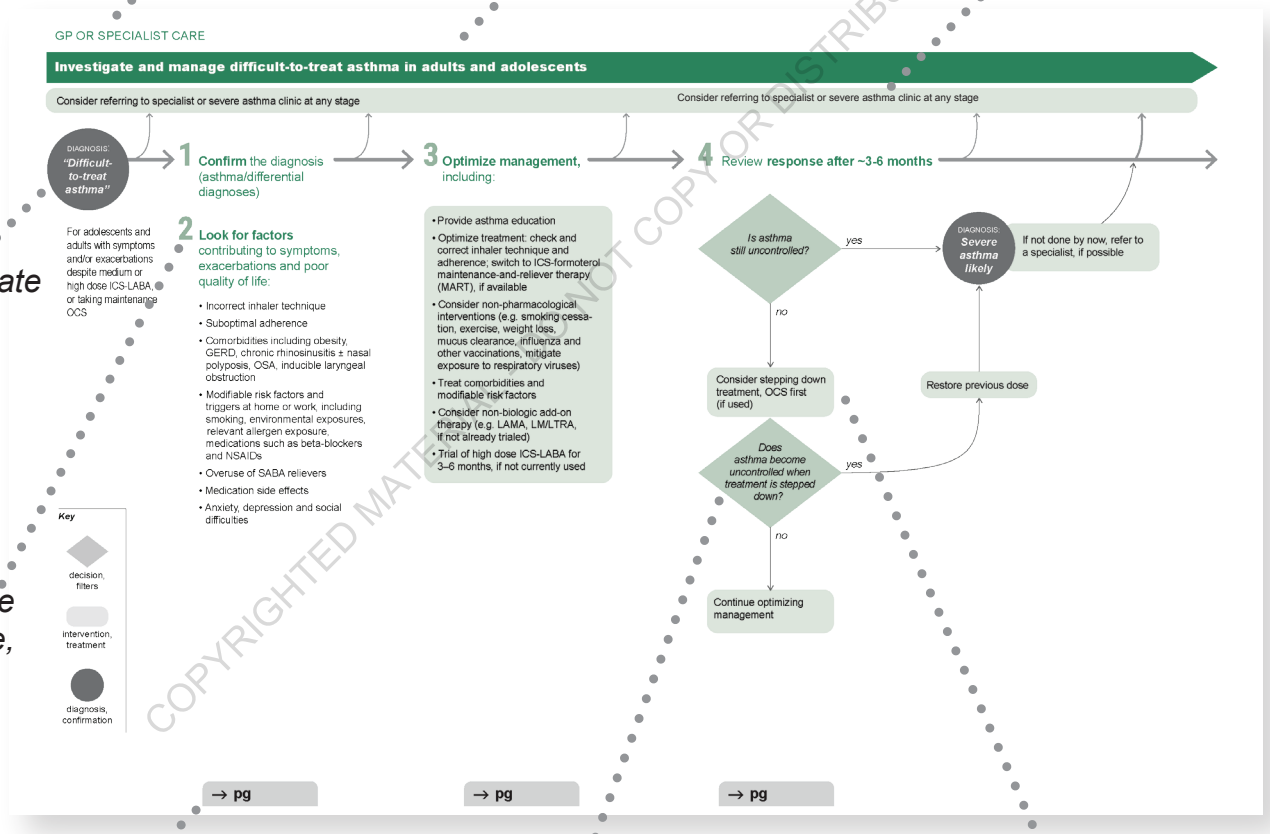
A **clinical decision tree** on pages 10–13 summarizes what to consider at each stage:

- **Sections 1–4 (green)** are for use in primary care and/or specialist care.
- **Sections 5–8 (blue)** are mainly relevant to respiratory specialists.
- **Sections 9–10 (brown)** are about maintaining ongoing collaborative care between the patient, primary care physician, specialist and other health professionals.

Locus of care: GP or specialist

Overall aim of the sections on this double page

Reminders about ongoing issues



Circles indicate diagnosis

Key section of the decision tree, numbered

Page number for more details

Diamonds indicate decision points

Colored boxes indicate treatment

Detailed information about each numbered stage starts on page 14.

"GINA 2026 Strategy Report Box" numbers in the text refer to boxes in the 2026 Strategy Report, available at **www.ginasthma.org**.

Definitions: uncontrolled, difficult-to-treat, and severe asthma

Understanding the definitions of difficult-to-treat and severe asthma starts with the concept of uncontrolled asthma.

Uncontrolled asthma includes one or both of the following:

- Poor symptom control (frequent symptoms or reliever use, activity limited by asthma, night waking due to asthma)
- Frequent exacerbations (≥2/year) requiring OCS, or serious exacerbations (≥1/year) requiring hospitalization.

Difficult-to-treat asthma is asthma that is uncontrolled despite prescribing of medium- or high-dose ICS with a second controller (usually a LABA) or with maintenance OCS, or that requires high-dose treatment to maintain good symptom control and reduce the risk of exacerbations.[1] It does not mean a "difficult patient". In many cases, poor control may be due to modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or an incorrect diagnosis.

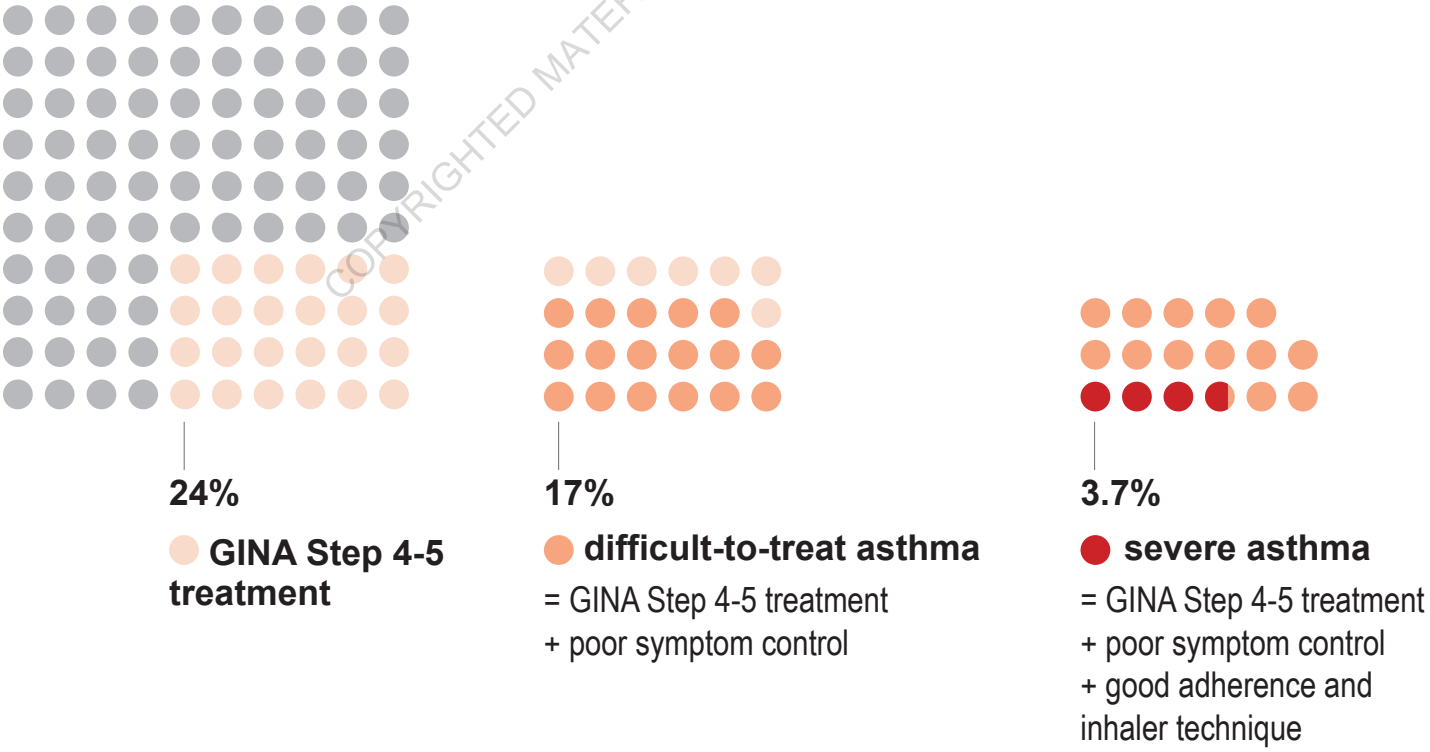
Severe asthma is a subset of difficult-to-treat asthma (Figure 1). It means asthma that is uncontrolled despite adherence with maximal optimized high-dose ICS-LABA treatment and management of contributory factors, or that worsens when high-dose treatment is decreased.[1] At present, therefore, "severe asthma" is a retrospective label. It is sometimes called "severe refractory asthma"[1] since it is defined by being relatively refractory to high-dose inhaled therapy. However, with the advent of biologic therapies, the word "refractory" is no longer appropriate.

Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.[1]

Prevalence: how many people have severe asthma?

A study in the Netherlands estimated that around 3.7% of asthma patients have severe asthma, based on the number of patients prescribed high-dose ICS-LABA, or medium- or high-dose ICS-LABA plus long-term OCS, who had poor symptom control (by Asthma Control Questionnaire) and had good adherence and inhaler technique (Figure 1).[2]

Figure 1. What proportion of adults have difficult-to-treat or severe asthma?



Data from the Netherlands, reported by Hekking et al (2015)[2]

Importance: the impact of severe asthma

The patient perspective

Patients with severe asthma experience a heavy burden of symptoms, exacerbations and medication side-effects. Frequent shortness of breath, wheeze, chest tightness and cough interfere with day-to-day living, sleeping, and physical activity, and patients often have frightening or unpredictable exacerbations (also called attacks or severe flare-ups).

Medication side-effects are particularly common and problematic with OCS,[3] which in the past were a mainstay of treatment for severe asthma. Adverse effects of long-term or frequent OCS include obesity, diabetes, osteoporosis and fragility fractures,[4] cataracts, hypertension and adrenal suppression; psychological side-effects such as depression and anxiety are particularly concerning for patients.[5] Even short-term use of OCS is associated with sleep disturbance, and increased risk of infection, fracture and thromboembolism.[6] Strategies to minimize need for OCS are therefore a high priority.

Severe asthma often interferes with family, social and working life, limits career choices and vacation options, and affects emotional and mental health. Patients with severe asthma often feel alone and misunderstood, as their experience is so different from that of most people with asthma.[5]

Adolescents with severe asthma

The teenage years are a time of great psychological and physiological development which can impact on asthma management. It is vital to ensure that the young person has a good understanding of their condition and treatment and appropriate knowledge to enable supported self-management. The process of transition from pediatric to adult care should help support the young person in gaining greater autonomy and responsibility for their own health and wellbeing. Severe asthma may improve over 3 years in approximately 30% of males and females.[7] The only reported predictor of asthma becoming non-severe is higher baseline blood eosinophils.[7] Studies with longer follow-up time are needed.

Healthcare utilization and costs

Severe asthma has very high healthcare costs due to medications, physician visits, hospitalizations, and the costs of OCS side-effects. In a UK study, healthcare costs per patient were higher than for type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD).[8] In a Canadian study, severe uncontrolled asthma was estimated to account for more than 60% of asthma costs.[9]

Patients with severe asthma and their families also bear a significant financial burden, not only for medical care and medications, but also through lost earnings and career choices.

Overview of decision tree for assessment and management of difficult-to-treat and severe asthma

The clinical decision tree (from p.10), summarizes a stage-by-stage, evidence-based approach to investigating and managing difficult-to-treat asthma in adults and adolescents, assessing and treating severe asthma phenotypes, and monitoring/adjusting severe asthma treatment. The decision tree is divided into three broad stages:

Stages 1–4 (green) are for use in primary care and/or specialist care.

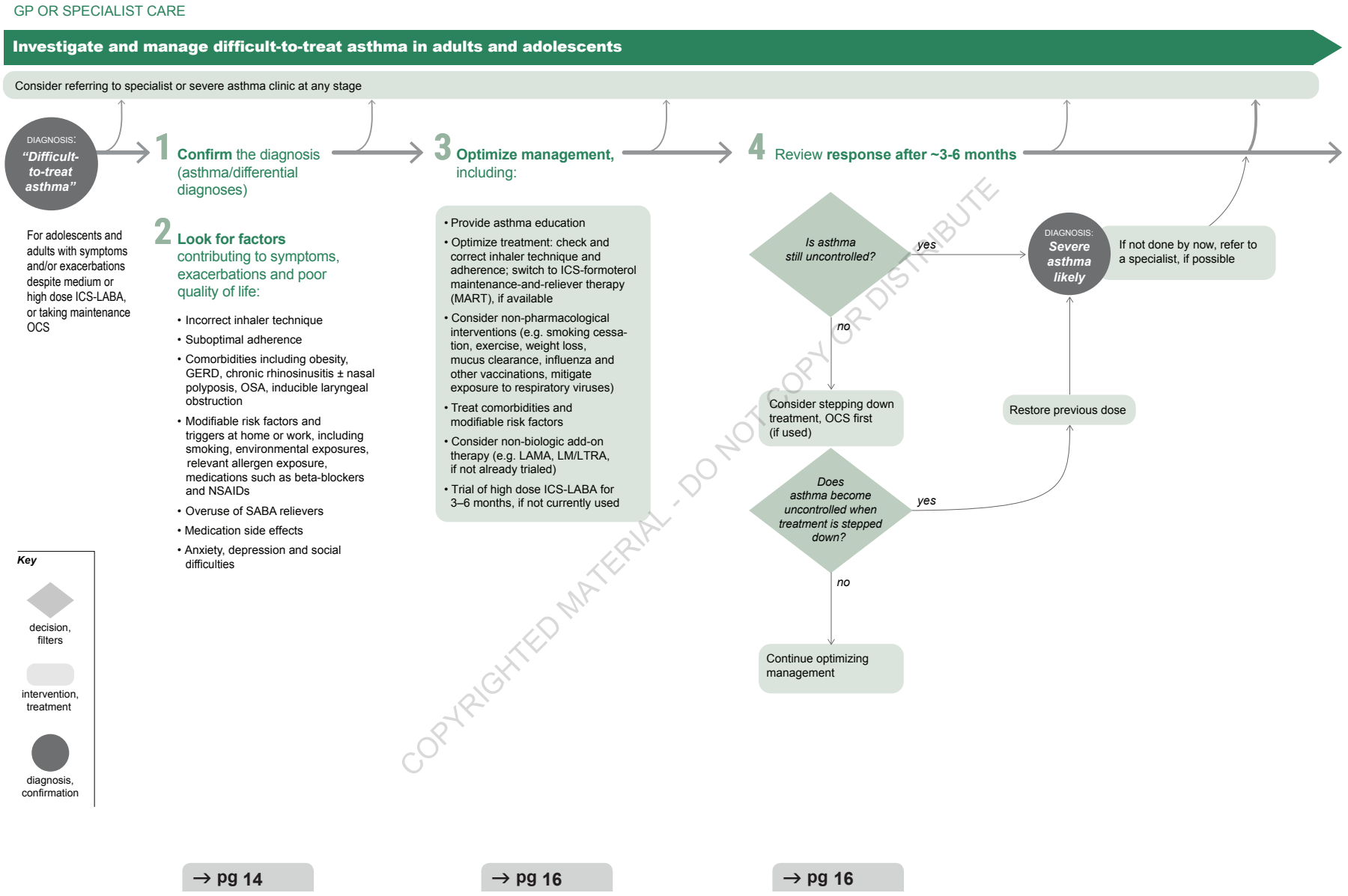
Stages 5–8 (blue) are mainly relevant to respiratory specialists.

Stages 9–10 (brown) are about maintaining ongoing collaborative care between the patient, primary care physician, specialist and other healthcare providers.

The Severe Asthma Guide and decision tree was designed in collaboration with experts in the translation of complex health information into visual formats.

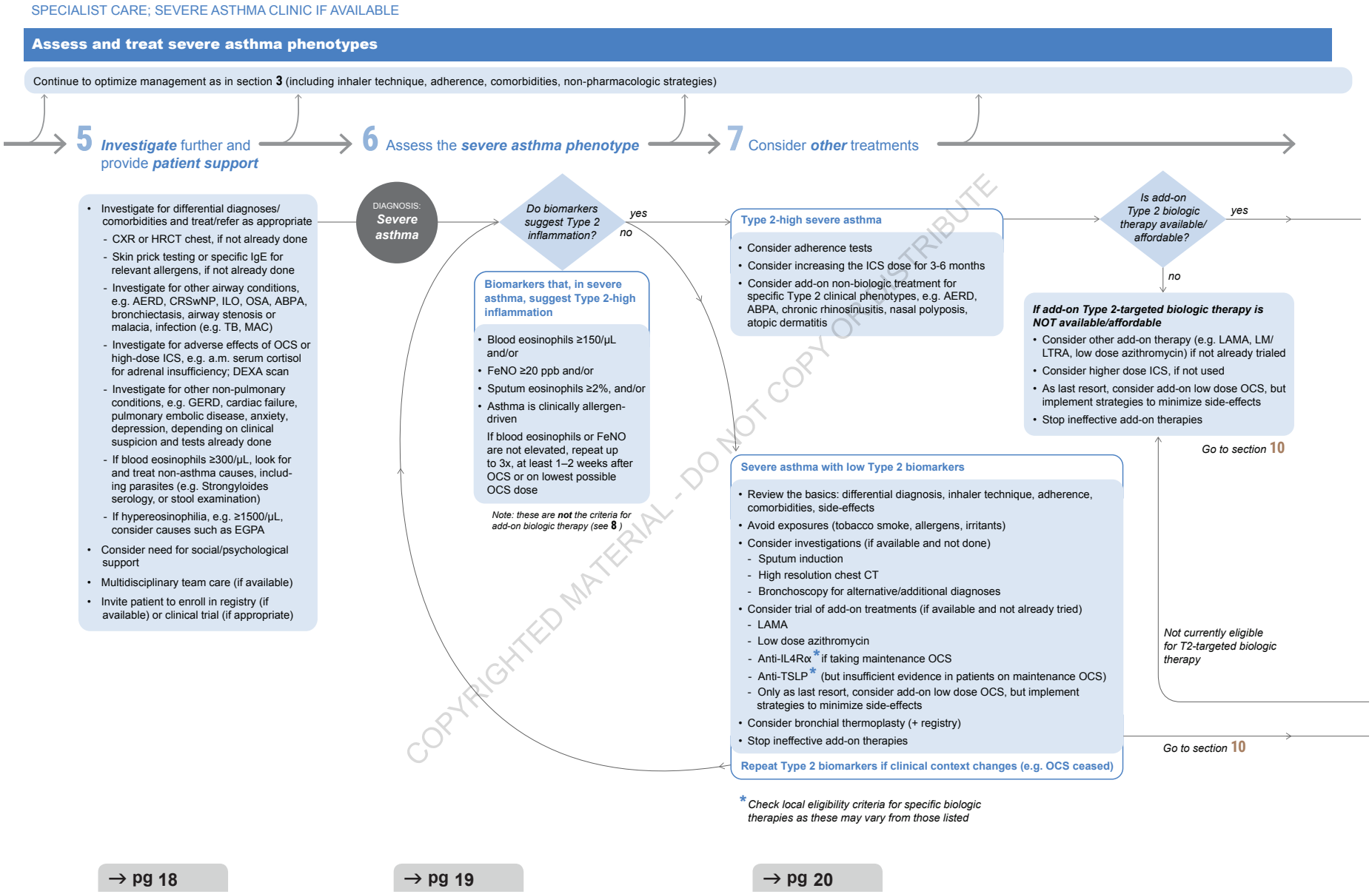
The decision tree is followed by more detailed information on each stage of assessment and management.

Figure 2. Decision tree – investigate and manage difficult to treat asthma in adult and adolescent patients



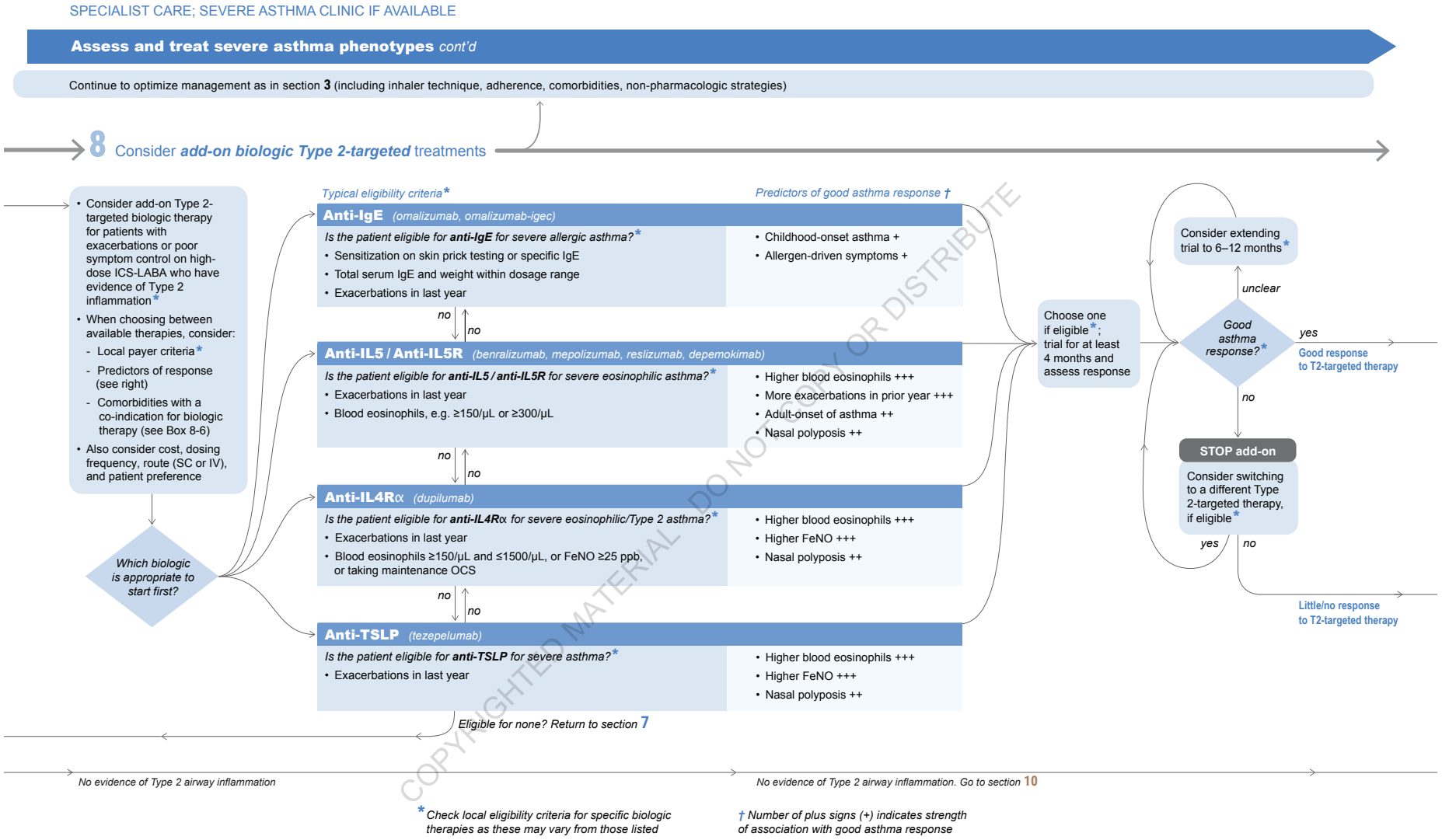
GERD: gastroesophageal reflux disease; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonists; LM: leukotriene modifiers; LTRA: leukotriene receptor antagonists; MART: maintenance-and-reliever therapy with ICS-formoterol; NSAIDs: non-steroidal anti-inflammatory drugs; OCS: oral corticosteroids; OSA: obstructive sleep apnea; SABA: short-acting beta2-agonist

Figure 3. Decision tree – assess and treat severe asthma phenotypes



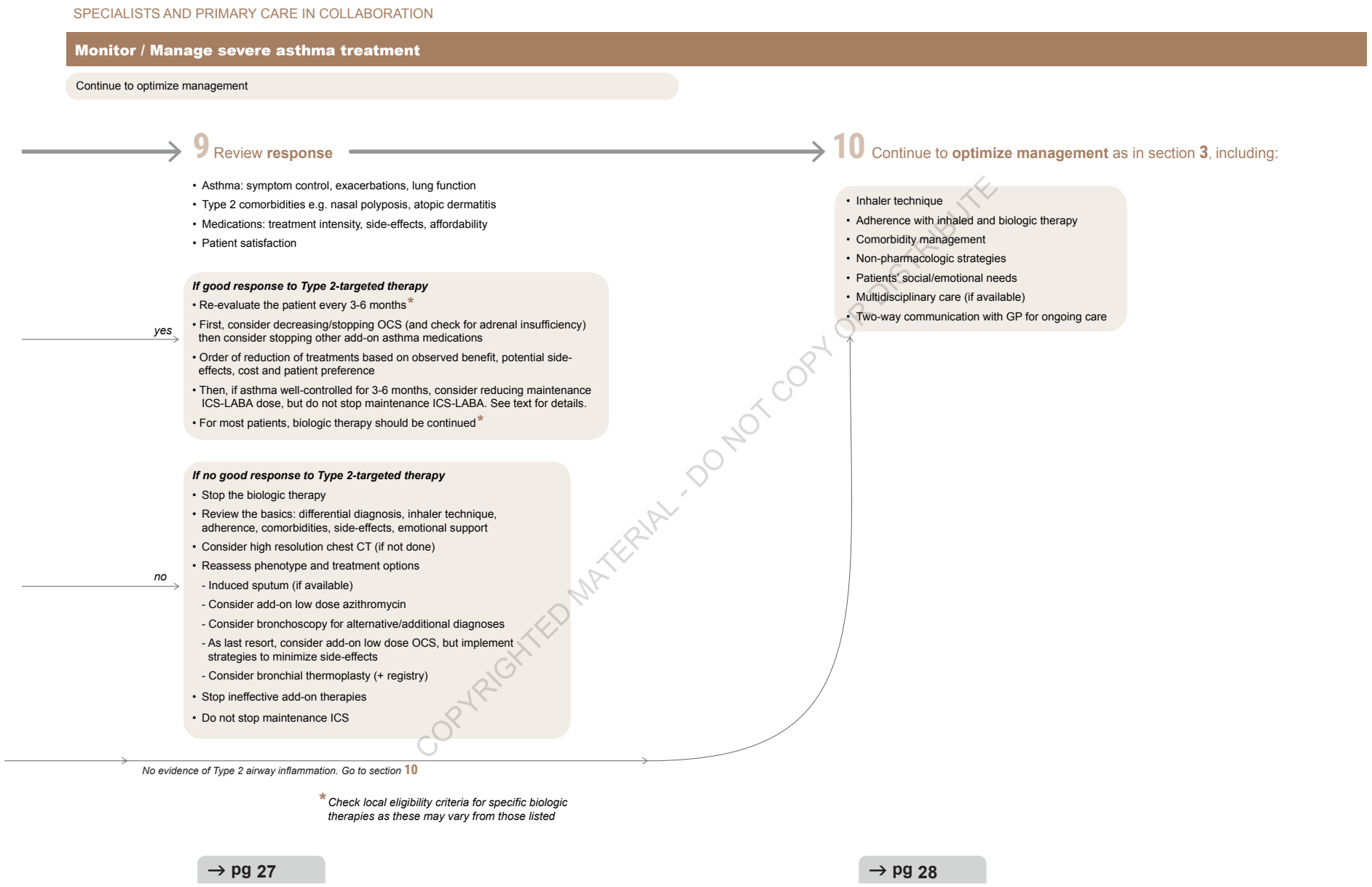
ABPA: allergic bronchopulmonary aspergillosis; AERD: aspirin-exacerbated respiratory disease; CRSwNP: chronic rhinosinusitis with nasal polyps; CXR: chest X-ray; DEXA: Dual-energy X-ray Absorptiometry; EGPA: eosinophilic granulomatosis with polyangiitis; FeNO: fractional exhaled nitric oxide; GERD: gastroesophageal reflux disease; HRCT: high resolution computed tomography; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; ILO: inducible laryngeal obstruction; LABA: long-acting beta2-agonist; LAMA: long-acting muscarinic antagonists; MAC: Mycobacterium avium complex; NSAIDs: non-steroidal anti-inflammatory drugs; OCS: oral corticosteroids; OSA: obstructive sleep apnea; SABA: short-acting beta2-agonist; TB: tuberculosis; TSLP: thymic stromal lymphopoietin.

Figure 4. Decision tree – consider add-on biologic Type 2-targeted treatments



FeNO: fractional concentration of exhaled nitric oxide; ICS: inhaled corticosteroids; Ig: immunoglobulin; IL: interleukin; IV: intravenous; LABA: long-acting beta2-agonist; OCS: oral corticosteroids; SC: subcutaneous; TSLP: thymic stromal lymphopoietin.

Figure 5. Decision tree – monitor and manage severe asthma treatment



CT: computed tomography; GP: general practitioner/family physician; ICS: inhaled corticosteroids; LABA: long-acting beta2-agonist; OCS: oral corticosteroids.

Investigate and manage difficult-to-treat asthma in adults and adolescents

1 Confirm the diagnosis (asthma or differential diagnoses)

Stages 1–5 can be carried out in primary or specialist care. A patient is classified as having difficult-to-treat asthma if they have persistent asthma symptoms and/or exacerbations despite prescribing of medium- or high-dose ICS with another controller such as LABA, or maintenance OCS, or require high-dose ICS-LABA treatment to maintain good symptom control and prevent exacerbations. Difficult-to-treat asthma does not mean a "difficult patient".

Consider referral to a specialist or severe asthma clinic at any stage, particularly if:

- There is difficulty confirming the diagnosis of asthma
- Patient has frequent urgent healthcare utilization
- Patient needs frequent or maintenance OCS
- Occupational asthma is suspected
- Patient has confirmed food allergy or a history of anaphylaxis, as this increases the risk of death
- Symptoms are suggestive of infective or cardiac cause
- Symptoms are suggestive of complications such as bronchiectasis
- Patient has multimorbidity.

Are the symptoms due to asthma?

Perform a careful history and physical examination to identify whether symptoms are typical of asthma, or are more likely due to an alternative diagnosis or comorbidity:

- **Dyspnea:** COPD, obesity, cardiac disease, deconditioning
- **Cough:** inducible laryngeal obstruction (also called vocal cord dysfunction [VCD]), upper airway cough syndrome (also called post-nasal drip), gastro-esophageal reflux disease (GERD), bronchiectasis, angiotensin-converting enzyme (ACE) inhibitors
- **Wheeze:** obesity, COPD, tracheobronchomalacia, VCD.

Investigate according to clinical suspicion and age (see GINA 2026 Strategy Report Box 1-3).

How can the diagnosis of asthma be confirmed?

Confirmation of the diagnosis is important, because in 12–50% of people assumed to have severe asthma, asthma is not found to be the correct diagnosis.[10] Perform spirometry, before and after bronchodilator, to assess baseline lung function and seek objective evidence of variable expiratory airflow. If initial bronchodilator responsiveness testing is negative (<200 mL or <12% increase in FEV_1), consider repeating after withholding bronchodilators or when symptomatic, or consider stepping controller treatment up or down before further investigations such as bronchial provocation testing (see GINA 2026 Strategy Report Box 1-4). Check full flow-volume curve to assess for upper airway obstruction.

If spirometry is not available, measure peak expiratory flow (PEF) before and after bronchodilator (highest of 3 PEF readings each time); an increase in PEF ≥20% supports the diagnosis of asthma. If spirometry is normal, provide the patient with a peak flow meter and diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (short-acting $beta_2$-agonist [SABA] for at least 6 hours, LABA for up to 2 days depending on duration of action).[11] Strategies for confirming the diagnosis of asthma in patients already taking ICS-containing treatment are shown in GINA 2026 Strategy Report Box 1-4.

Airflow limitation may be persistent in patients with longstanding asthma, due to remodeling of the airway walls, or limited lung development in childhood. It is important to document lung function when the diagnosis of asthma is first made. Specialist advice should be obtained if the history is suggestive of asthma, but the diagnosis cannot be confirmed by spirometry.

2 Look for factors contributing to symptoms and exacerbations

Systematically consider factors that may be contributing to uncontrolled symptoms or exacerbations, or poor quality of life, and that can be treated.

The most important modifiable factors include:

- **Incorrect inhaler technique** (seen in up to 80% patients): ask the patient to show you how they use their inhaler; compare with a checklist or video.
- **Suboptimal adherence** (up to 75% asthma patients): Ask empathically about frequency of use (e.g., "Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1 day a week, 2, 3 or more?" or "Do you find it easier to remember your inhaler in the morning or the evening?" (see GINA 2026 Strategy Report Box 5-3). Ask about barriers to medication use, including cost, and concerns about necessity or side-effects. Check dates on inhalers and view dispensing data, if available. A FeNO suppression test, i.e., reduced FeNO during a week of high-dose ICS, added to usual maintenance ICS-LABA, can identify patients with poor adherence.[12,13] Electronic inhaler monitoring, if available, can be helpful in screening for poor adherence, in some cases avoiding the need for biologic therapy.[14]
- **Comorbidities:** Review history and examination for comorbidities that can contribute to respiratory symptoms, exacerbations, or poor quality of life. These include anxiety and depression, obesity, deconditioning, chronic rhinosinusitis, inducible laryngeal obstruction, GERD, COPD, obstructive sleep apnea, bronchiectasis, cardiac disease, and kyphosis due to osteoporosis. Investigate according to clinical suspicion. For more information on managing multimorbidity, including COPD, see GINA 2026 Strategy Report Section 6 and Section 7.
- **Modifiable risk factors and triggers:** Identify factors that increase the risk of exacerbations, e.g., smoking, vaping, environmental tobacco exposure, other environmental exposures at home or work including allergens (if sensitized), indoor and outdoor air pollution, molds and noxious chemicals, and medications such as beta-blockers or non-steroidal anti-inflammatory drugs (NSAIDs). For allergens, check for sensitization using skin prick testing or specific immunoglobin (Ig) E.
- **Regular or over-use of SABAs:** Regular SABA use causes beta-receptor down-regulation and reduction in response,[15] leading in turn to greater use. SABA over-use may also be habitual. Dispensing of ≥3 SABA canisters per year (corresponding to average use more than daily) is associated with increased risk of emergency department visit or hospitalization independent of severity,[16,17] and dispensing of ≥12 canisters per year (one a month) is associated with substantially increased risk of death.[17,18] Risks are higher with nebulized SABA.[19]
- **Anxiety, depression and social and economic problems:** These are very common in asthma, particularly in difficult asthma[5] and contribute to symptoms, impaired quality of life, and poor adherence.
- **Medication side-effects:** Systemic effects, particularly with frequent or continuous OCS, or long-term high-dose ICS may contribute to poor quality of life and increase the likelihood of poor adherence. Local side-effects of dysphonia or candidiasis may occur with high-dose or potent ICS, especially if inhaler technique is poor. Consider drug interactions including risk of adrenal suppression with use of P450 inhibitors such as itraconazole.

3 Review and optimize management

Review and optimize treatment for asthma, and for comorbidities and risk factors identified at Stage 2.

- **Provide asthma self-management education**, and confirm that patient has (and knows how to use) a personalized written or electronic asthma action plan. Refer to an asthma educator if available.
- **Optimize asthma medications:** Confirm that the inhaler is suitable for the patient; check and correct inhaler technique with a physical demonstration and teach-back method, check inhaler technique again at each visit.[20] Address suboptimal adherence, both intentional and unintentional.[21] Switch to ICS-formoterol maintenance-and-reliever therapy (MART) if available, to reduce the risk of exacerbations.[22] Electronic inhaler monitoring with feedback can improve adherence.[14]
- **Consider non-pharmacologic add-on therapy**, e.g., smoking cessation, physical exercise,[23] healthy diet, weight loss, mucus clearance strategies, vaccinations including influenza and respiratory syncytial virus (RSV), pulmonary rehabilitation and breathing exercises. Pulmonary rehabilitation is recommended for all patients who have limited exercise tolerance, or have dyspnea due to persistent airflow limitation. Although allergen avoidance strategies may be beneficial for some sensitized patients (Evidence B), they are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit (Evidence D). For details about these and other non-pharmacologic strategies see text following GINA 2026 Strategy Report Box 3-6.
- **Treat comorbidities and modifiable risk factors** identified in Stage 2 of the decision tree, where there is evidence for benefit; however, there is no evidence to support routine treatment of asymptomatic GERD. Avoid medications that make asthma worse (beta-blockers including eye-drops, aspirin and other NSAIDs in patients with aspirin-exacerbated respiratory disease). Refer for management of mental health problems, if relevant. Consider exposure mitigation for respiratory viruses (physical distancing from contacts with respiratory infections, mask wearing). For more details on multimorbidity, see GINA 2026 Strategy Report Section 6, including information about treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP). However, **do not delay referral** for specialist assessment if the person has made unsuccessful attempts at reducing risk factors (e.g. smoking cessation, weight loss). The presence of CRSwNP in a patient with difficult-to-treat asthma should prompt early referral, given its association with severe asthma, the risk of additional exposure to OCS, and the potential benefit for both severe asthma and CRSwNP with some biologic therapies (see Stage 8, p.21).
- **Consider trial of non-biologic medication** added to medium dose ICS, e.g., LABA, LAMA, LTRA if not already tried. Note concerns about neuropsychiatric adverse effects with montelukast.[24]
- **Consider short-term (3–6 months) trial of high-dose ICS-LABA**, if not currently used.

4 Review response after ~3–6 months

Schedule a review visit to assess the response to the above interventions. Timing of the review visit depends on clinical urgency and what changes to treatment have been made.

When assessing the response to treatment, specifically review:

- Symptom control (symptom frequency, SABA reliever use, night waking due to asthma, activity limitation)
- Exacerbations since previous visit, and how they were managed
- Medication side-effects
- Inhaler technique and adherence
- Lung function
- Patient satisfaction and concerns.

→ *Is asthma still uncontrolled, despite optimized therapy?*

YES: If asthma is still uncontrolled, the diagnosis of severe asthma is likely. If not done by now, refer the patient to a specialist or severe asthma clinic if possible.

NO: If asthma is now well controlled, consider stepping down treatment. Start by decreasing/ceasing OCS first (if used), checking for adrenal insufficiency, then consider removing other add-on therapy, then decrease ICS dose, but do not stop ICS. See GINA 2026 Strategy Report Box 4-13 for how to gradually down-titrate treatment intensity.

→ *Does asthma become uncontrolled when treatment is stepped down?*

YES: If asthma symptoms become uncontrolled or an exacerbation occurs when high-dose treatment is stepped down, the diagnosis of severe asthma is likely. Restore the patient's previous dose to regain good asthma control, and refer to a specialist or severe asthma clinic, if possible, if not done already.

NO: If symptoms and exacerbations remain well controlled despite treatment being stepped down, the patient does not have severe asthma. Continue optimizing management.

5 Investigate further and provide patient support

Further assessment and management should be done by a specialist, preferably in a multidisciplinary severe asthma clinic if available. The team may include a certified asthma educator and healthcare providers from fields such as speech pathology, otorhinolaryngology, social work and mental health.

What other tests may be considered at the specialist level?

Additional investigations may be appropriate for identifying less-common comorbidities and differential diagnoses contributing to symptoms and/or exacerbations.

Tests should be based on clinical suspicion, and may include:

- Chest X-ray or high-resolution CT chest, if not already done, including for identification of mucus plugging, bronchiectasis, and emphysema
- In patients with asthma who have early-onset persistent airflow limitation, or have emphysema on CT scan with little smoking history, consider testing for alpha-1 antitrypsin deficiency
- Allergy testing for clinically relevant allergens: skin prick test or specific IgE, if not already done
- Investigations for other airway/lung conditions, e.g., aspirin-exacerbated respiratory disease (AERD), CRSwNP, inducible laryngeal obstruction, obstructive sleep apnea, allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis, tracheobronchomalacia, and infection (e.g., TB, mycobacterium avian complex [MAC]), based on clinical suspicion and other findings
- Bone density scan, because of risk of osteoporosis with maintenance or frequent OCS or long-term high dose ICS.[25]
- Investigations for other adverse effects of OCS or high-dose ICS, e.g., morning serum cortisol for adrenal insufficiency
- Investigations for other non-pulmonary conditions that may be contributing to respiratory symptoms, exacerbations or poor quality of life, e.g., GERD, cardiac failure, pulmonary embolic disease, anxiety, depression, depending on clinical suspicion and tests already done.

If blood eosinophils are ≥300/μL, look for and treat non-asthma causes, including parasites (e.g., Strongyloides serology or stool examination), because parasitic infection may be the cause of the blood eosinophilia, and because OCS or biologic therapy in a patient with untreated parasitic infection could potentially lead to disseminated disease. Chronic Strongyloides infection is usually asymptomatic.[26]

If hypereosinophilia is found, e.g., blood eosinophils ≥1500/μL, consider causes such as eosinophilic granulomatosis with polyangiitis (EGPA).

If other causes of the patient's symptoms & exacerbations have been excluded, the diagnosis of severe asthma is confirmed.

Consider need for social/psychological support

Refer patients to support services, where available, to help them deal with the emotional, social and financial burden of asthma and its treatment, including during and after severe exacerbations.[5] Consider the need for psychological or psychiatric referral, including for patients with anxiety and/or depression.

Involve multidisciplinary team care (if available)

Multidisciplinary assessment and treatment of patients with severe asthma increases identification of comorbidities and improves outcomes.[27]

Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

Systematic collection of data will help in understanding the mechanisms and burden of severe asthma. There is a need for pragmatic clinical trials in severe asthma, including studies comparing two or more active treatments. Participants in randomized controlled trials designed for regulatory purposes may not necessarily be representative of patients seen in clinical practice. For example, a registry study found that over 80% of patients with severe asthma would have been excluded from key studies evaluating biologic therapy.[28]

6 Assess the severe asthma phenotype

The next stage is to assess the patient's inflammatory phenotype – is there evidence of Type 2 inflammation?

What is Type 2 inflammation?

Evidence of Type 2 inflammation is found in most people with severe asthma. It is often characterized by the presence of cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are produced by the adaptive immune system on recognition of allergens. The adaptive immune system may also be activated by viruses, bacteria and irritants that stimulate it via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by elevated sputum and blood eosinophils or increased fractional exhaled nitric oxide (FeNO), and it may be accompanied by atopy and elevated IgE, whereas patients without evidence of Type 2 inflammation often have increased neutrophils.[29]

A single low blood eosinophil count does not rule out Type 2 asthma, and may reflect fluctuating levels. In one study, patients with fluctuating blood eosinophil counts had similar exacerbation rates as those with persistently high levels.[30]

In many patients with asthma, Type 2 inflammation rapidly improves when an ICS is taken regularly and correctly;[13,14] these patients do not have severe asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high-dose ICS. It may respond to OCS, but this should be avoided because of their serious adverse effects.[3,31]

In adult patients with uncontrolled asthma despite medium- or high-dose ICS plus LABA or other controllers, a history of exacerbations in the previous year, higher blood eosinophil counts and higher FeNO levels are associated with a greater risk of severe exacerbations.[32,33] However, there are multiple sources of variation in blood eosinophils[34,35] and in FeNO,[36] which may impact on the ability to document a patient's eligibility for Type 2-directed biologic therapy (see GINA 2026 Strategy Report Appendix A).

Could the patient have refractory or underlying Type 2 inflammation?

The possibility of refractory Type 2 inflammation should be considered if any of the following are found while the patient is taking high-dose ICS or daily OCS:

- Blood eosinophils ≥150/μL
- FeNO ≥20 ppb
- Sputum eosinophils ≥2%
- Asthma is clinically allergen-driven.

Patients requiring maintenance OCS may also have underlying Type 2 inflammation. However, biomarkers of Type 2 inflammation (blood eosinophils, sputum eosinophils and FeNO) are often suppressed by OCS. If possible, therefore, these tests should be performed before starting OCS (a short course, or maintenance treatment), or at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose.

There are multiple causes of variation in blood eosinophil count and FeNO, summarized in GINA 2026 Strategy Report Appendix A. These include time of day, with blood eosinophils higher in the morning and FeNO higher in the afternoon. One study of patients with uncontrolled asthma taking medium- to high-dose ICS-LABA found that 65% had a shift in their blood eosinophil category over 48–56 weeks.[37] Therefore, consider repeating blood eosinophils and FeNO up to 3 times (e.g., when asthma worsens, before giving OCS, or at least 1–2 weeks after a course of OCS, or on the lowest possible OCS dose), before assuming that the patient is not eligible for Type 2-targeted therapy. A pause of even two days in OCS dosing may allow the blood eosinophil count to reach the eligibility threshold.[38]

The above criteria are suggested for initial assessment; those for blood eosinophils and FeNO are based on the lowest levels associated with response to some biologics. They are not the criteria for eligibility for Type 2-targeted biologic therapy, which may differ – see Stage 8 (p.21) and local regulatory and payer criteria.

Why is the inflammatory phenotype assessed on high dose ICS?

- Most randomized controlled trial (RCT) evidence about Type 2 targeted biologics is in such patients.
- Modifiable ICS treatment problems such as poor adherence and incorrect inhaler technique are common causes of uncontrolled Type 2 inflammation.
- Currently, the high cost of biologic therapies generally precludes their widespread clinical use in patients whose symptoms or exacerbations and Type 2 biomarkers are found to respond to ICS when it is taken correctly.

7.1 Consider other treatments if there is NO evidence of Type 2 inflammation

If the patient has no evidence of persistent Type 2 inflammation (Stage 6):

- Review the basics for factors that may be contributing to symptoms or exacerbations: differential diagnosis, inhaler technique, adherence, comorbidities, medication side-effects (Stage 2).
- Recommend avoidance of relevant exposures (tobacco smoke, pollution, allergens if sensitized and there is evidence of benefit from withdrawal, irritants, infections). Ask about exposures at home and at work.
- Consider additional diagnostic investigations (if available and not already done): sputum induction to confirm inflammatory phenotype, high resolution chest CT, bronchoscopy to exclude unusual comorbidities or alternative diagnoses such as tracheobronchomalacia or sub-glottic stenosis; functional laryngoscopy for inducible laryngeal obstruction.
- Consider a trial of add-on treatment if available and not already tried (but check local eligibility and payer criteria for specific therapies as they may vary from those listed):
    - LAMA[39-41] (note that doses of triple therapy for asthma may differ from those approved for COPD)
    - Low-dose azithromycin (adults),[42,43] but first check sputum for atypical mycobacteria, check ECG for long QTc (and re-check after a month on treatment), and consider potential for antibiotic resistance.
    - Anti-IL4Rα if taking maintenance OCS (see stage 8 for more details)
    - Anti-thymic stromal lymphopoietin (TSLP) (but insufficient evidence in patients taking maintenance OCS; see Stage 8 for more details)
    - As a last resort, consider add-on low dose OCS, but implement strategies such as alternate-day treatment to help reduce the dose further and minimize side-effects.
- Consider bronchial thermoplasty, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.[44,45]
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see Stages 3 and 10).
- Repeat Type 2 biomarkers if the clinical context changes, e.g., cessation or reduction in OCS dose.

7.2 Consider non-biologic options if there IS evidence of type 2 inflammation

For patients with elevated Type 2 biomarkers despite high-dose ICS (see Stage 5), consider non-biologic options first, given the current high cost of biologic therapy:

- **Assess adherence objectively** by monitoring of prescribing or dispensing records, blood prednisone levels,[46] or electronic inhaler monitoring.[47] Suppression of high FeNO after 5 days of directly observed therapy is an indicator of past poor adherence,[13] and was found in almost two-thirds of patients with difficult-to-treat asthma.[12] In one study, electronic monitoring of adherence and inhaler technique, with feedback to patients, improved adherence and reduced the proportion of patients who needed escalation to biologic therapy.[14]

- **Consider increasing the ICS dose** for 3–6 months, and review again.
- **Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes.** (see GINA 2026 Strategy Report Section 6). For example, for AERD, consider add-on LTRA and possibly aspirin desensitization. For ABPA, consider add-on OCS ± anti-fungal agent. For chronic rhinosinusitis with or without nasal polyps, consider intensive intranasal corticosteroids; surgical advice may be needed. For patients with atopic dermatitis, topical steroidal or non-steroidal therapy may be helpful. Allergen immunotherapy may sometimes be used in severe asthma, but only after asthma has been well controlled, to minimize the risk of severe adverse reactions (see GINA 2026 Strategy Report Section 4). Allergen immunotherapy extracts for subcutaneous immunotherapy (SCIT) should only be prepared and administered by clinicians skilled in immunotherapy.

7.3 Is Type 2-targeted biologic therapy available and affordable?

If NOT:

- Consider higher dose ICS-LABA, if not used.
- Consider other add-on therapy, e.g. LAMA, LTRA, low dose azithromycin, if not already used.
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects.
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see Stages 3 and 10).

Consider type 2-targeted biologic therapies

8 Consider add-on biologic Type 2-targeted treatments

If available and affordable, consider an add-on Type 2 targeted biologic for patients with exacerbations and/or poor symptom control despite taking at least high-dose ICS-LABA, and who have allergic or eosinophilic Type 2-high severe asthma or need maintenance OCS. Where relevant, test for parasitic infection, and treat if present, before commencing treatment (see Stage 5).

Consider whether to start first with anti-IgE, anti-IL5/5Rα, anti-IL4Rα or anti-TSLP. When choosing between available therapies, consider the following:

- Does the patient satisfy local payer eligibility criteria?
- Type 2 comorbidities such as atopic dermatitis, nasal polyps that may have co-indications for biologic therapy (see below and Table 1).
- Clinical history suggesting allergen-triggered symptoms
- Predictors of asthma response (see below)
- Cost
- Dosing frequency
- Delivery route (IV or SC; potential for self-administration)
- Patient preference.

Always check local payer eligibility criteria for biologic therapy, as they may vary substantially. However, GINA recommends the use of biologic therapy only for patients with severe asthma, and only after treatment has been optimized. For any biologic therapy, ensure that the manufacturer's and/or regulator's instructions for storage, administration and the duration of monitoring post-administration are followed.

Provide the patient with advice about what to do if they experience any adverse effects, including hypersensitivity reactions. Omalizumab and biosimilar omalizumab-igec injections contain polysorbate, which may induce allergic reactions in some patients. GINA suggests that the first dose of asthma biologic therapy should not be given on the same day as a vaccine, so that adverse effects of either can be more easily distinguished.

Provide practical advice for patients, e.g., allow the refrigerated syringe or pen to come to room temperature before injecting the biologic, as this reduces pain. For travel, some biologic therapies can be carried without refrigeration for up to 14 days; check local product information and airline advice about travelling with sharps.

There is an urgent need for head-to-head comparisons of different biologics in patients eligible for more than one biologic.

→ *Add-on anti-IgE for severe allergic asthma*

Regulatory approvals for severe asthma may include: omalizumab and biosimilar omalizumab-igec for ages ≥6 years, given by SC injection every 2–4 weeks, with dose based on weight and serum IgE. Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: binds to Fc part of free IgE, preventing binding of IgE to FcƐR1 receptors, reducing free IgE and down-regulating receptor expression.

Eligibility criteria (in addition to criteria for severe asthma) may vary between payers or by age-group, but often include:

- Sensitization to inhaled allergen(s) on skin prick testing or specific IgE
- Total serum IgE and body weight within local dosing range, and
- More than a specified number of exacerbations within the last year.

Outcomes: Meta-analysis of RCTs in severe allergic asthma: anti-IgE led to 44% decrease in severe exacerbations, and improved quality of life; improvements in symptom control and lung function were statistically significant but less than clinically important differences.[48] No double-blind RCTs of OCS-sparing effect. In a meta-analysis of observational studies in patients with severe allergic asthma, there was a 59% reduction in exacerbation rate, a 41% reduction in the proportion of patients receiving maintenance OCS, and a significant improvement in symptom control.[49] A registry study of omalizumab in pregnancy found no increased risk of congenital malformations.[50]

Potential predictors of good asthma response to omalizumab or biosimilar omalizumab-igec:

- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms.

Baseline IgE level does not predict likelihood of response to anti-IgE.[51] In two large observational studies, exacerbations were reduced with both low or high blood eosinophils[52-54] or with both low or high FeNO.[54]

Additional indications for anti-IgE may include CRSwNP, chronic spontaneous (idiopathic) urticaria, and IgE-mediated food allergy. See Table 1 for doses and age-groups. Check local payer details, as they may differ.

In patients with nasal polyps, omalizumab improved subjective and objective nasal outcomes[55] (see GINA 2026 Strategy Report Section 6).

Adverse effects: injection site reactions, anaphylaxis in approximately 0.2% patients.[56] In adults, long-term safety and efficacy of omalizumab have been reported over up to 5 years of treatment.[57]

Suggested initial trial for severe asthma: at least 4 months

→ *Add-on anti-IL5 or anti-IL5Rα for severe eosinophilic asthma*

Regulatory approvals for severe asthma may include:

- For ages ≥12 years: mepolizumab (anti-IL5), 100 mg by SC injection every 4 weeks, or benralizumab (anti-IL5 receptor α), 30 mg by SC injection every 4 weeks for 3 doses then every 8 weeks, or depemokimab (anti-IL5), 100 mg by SC injection every 26 weeks
- For ages ≥18 years: reslizumab (anti-IL5), 3 mg/kg by IV infusion every 4 weeks
- For ages 6–11 years, mepolizumab (anti-IL5), 40 mg by SC injection every 4 weeks.

Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: mepolizumab, depemokimab and reslizumab bind circulating IL-5; benralizumab binds to IL-5 receptor alpha subunit leading to apoptosis (cell death) of eosinophils.

Eligibility criteria (in addition to criteria for severe asthma): these vary by product and between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- Blood eosinophils above locally specified level (e.g. ≥150 or ≥300/µl). There is sometimes a different eosinophil cut-point for patients taking OCS.

Outcomes: Meta-analysis of RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5Rα led to 47–54% reduction in severe exacerbations. Improvements in lung function and symptom control were statistically significant,[58] but less than clinically important differences. Similar results were seen in placebo-controlled studies of depemokimab (48–58% reduction in severe exacerbations, with less than clinically important differences in symptom control and lung function).[59] There was a clinically important improvement in quality of life with mepolizumab.[58] All anti-IL5/5Rα biologics reduced blood eosinophils; almost completely with benralizumab.[60] In post hoc analyses, clinical outcomes with mepolizumab or benralizumab were similar in patients with eosinophilic asthma with and without an allergic phenotype.[61,62] However, in patients with non-severe younger-onset allergic asthma, mepolizumab and benralizumab did not attenuate either the allergen-induced early or late asthmatic response, or airway hyperresponsiveness to methacholine.[63] In patients taking OCS, median OCS dose was able to be reduced by approximately 50% with mepolizumab[64] or benralizumab,[65] compared with placebo. In urban children aged 6 years and older with eosinophilic exacerbation-prone asthma, an RCT showed a reduction in the number of exacerbations with subcutaneous mepolizumab versus placebo.[66] No differences were seen in lung function, a composite asthma score (CASI), or physician–patient global assessment.[66] For adults with severe eosinophilic asthma, analysis of a depemokimab study suggested that switching to it may be considered for patients with a good response to mepolizumab, but not for patients with a good response to benralizumab.[67] More studies are needed.

Potential predictors of good asthma response to anti-IL5 or anti-IL5Rα:

- Higher blood eosinophils (strongly predictive)[68]
- Higher number of severe exacerbations in previous year (strongly predictive)[68]
- Adult-onset asthma[69,70]
- Nasal polyps[62]
- Maintenance OCS at baseline[62,70]
- Low lung function (FEV_1 <65% predicted in one study).[70]

Additional indications for anti-IL5 or anti-IL5Rα may include mepolizumab for EGPA and hypereosinophilic syndrome, benralizumab for EGPA, mepolizumab and depemokimab for CRSwNP, and mepolizumab for COPD with an eosinophilic phenotype. See Table 1 for doses and age-groups. Check local payer details, as they may differ.

In patients with nasal polyps, mepolizumab[71,72] and depemokimab[73] improved subjective and objective outcomes and reduced the need for surgery, and in patients with nasal polyps and severe eosinophilic asthma, benralizumab improved subjective outcomes for both conditions and improved quality of life.[74] See GINA 2026 Strategy Report Section 6 for more details about treatment of nasal polyps.

Adverse effects: In adults, injection site reactions, anaphylaxis (rare); adverse events generally similar between active and placebo groups. In children, more skin/subcutaneous tissue and nervous system disorders (e.g., headache, dizziness, syncope) reported with mepolizumab than placebo.[66] In adults, long-term safety and efficacy of mepolizumab and benralizumab have been reported for more than 5 years of treatment.[75,76] No data are available yet for outcomes of pregnancy in women treated with depemokimab.

Suggested initial trial for severe asthma: at least 4 months (6 months for depemokimab).

→ *Add-on anti-IL4Rα for severe eosinophilic/Type 2 asthma or patients requiring maintenance OCS*

Regulatory approvals for severe asthma may include:

- For ages ≥12 years: dupilumab (anti-IL4 receptor α), 200 mg or 300 mg by SC injection every 2 weeks for severe eosinophilic/Type 2 asthma
- For ages ≥12 years: dupilumab 300 mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis or CRSwNP
- For children 6–11 years with severe eosinophilic/Type 2 asthma by SC injection, with dose and frequency depending on weight.

Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: binds to interleukin-4 (IL-4) receptor alpha, blocking both IL-4 and IL-13 signaling

Eligibility criteria (in addition to criteria for severe asthma): these may vary between payers or by age-group, but often include:

- More than a specified number of severe exacerbations in the last year
- Type 2 biomarkers above a specified level (e.g. blood eosinophils ≥150/μL and ≤1500/μL; or FeNO ≥25 ppb) OR requirement for maintenance OCS.

Outcomes: Meta-analysis of RCTs in patients with uncontrolled severe asthma (ACQ-5 ≥1.5) and at least one exacerbation in the last year: anti-IL4Rα led to 56% reduction in severe exacerbations; improvements in quality of life, symptom control and lung function were statistically significant,[77] but less than the clinically important differences. In a post hoc analysis, clinical outcomes were similar in patients with allergic and non-allergic phenotype at baseline.[78] In patients with OCS-dependent severe asthma, without minimum requirements for blood eosinophil count or FeNO, the median reduction in OCS dose was 50% greater with anti-IL4Rα than with placebo.[79] Changes were maintained through 2 years of follow-up.[80] In children 6–11 years with eosinophilic/Type 2 asthma (excluding children taking maintenance OCS), dupilumab reduced severe exacerbation rate and increased lung function.[81] In an open-label extension study, the decrease in severe exacerbations among children who commenced dupilumab after 1 year of placebo was similar to that seen in those who received dupilumab from the start, but improvement in lung function was lower among those who were taking medium-dose ICS.[82]

Potential predictors of good asthma response to dupilumab:

- Higher blood eosinophils (strongly predictive)[83] including in children[84]
- Higher FeNO (strongly predictive)[83] including in children.[84]

Among adults with moderate-severe asthma and blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb, there was greater improvement in severe exacerbations and in pre-bronchodilator FEV_1 with dupilumab in those with asthma onset ≥18 years, but greater improvement in lung function in those with asthma duration <20 years.[85]

Additional indications for dupilumab may include moderate-to-severe atopic dermatitis, chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyps, COPD with chronic bronchitis and an eosinophilic phenotype, and eosinophilic esophagitis (see Table 1 for doses and age-groups). Check local payer details, as they may differ.

In patients with chronic rhinosinusitis with nasal polyps, dupilumab improved subjective and objective outcomes and reduced the need for OCS or for sinus surgery.[86,87] GINA 2026 Strategy Report Section 6 for more details about nasal polyps.

Adverse effects: injection-site reactions; transient blood eosinophilia (occurs in 4–13% of patients); rare cases of EGPA may be unmasked following reduction/cessation of OCS treatment on dupilumab. Anti-IL4Rα is not suggested for patients with baseline or historic blood eosinophils >1,500 cells/μL because of limited evidence (such patients were excluded from Phase III trials). In adults, safety and efficacy of dupilumab have been reported for over 5 years of treatment[82,88] and, in children aged 6–11 years, for up to 2 years of treatment.[82]

Suggested initial trial for severe asthma: at least 4 months

→ *Add-on anti-TSLP for severe asthma*

Regulatory approvals for severe asthma may include: For ages ≥12 years: tezepelumab (anti-TSLP), 210 mg by SC injection every 4 weeks. Self-administration may be an option. Check local payer criteria, as they may differ from these.

Mechanism: Tezepelumab binds circulating TSLP, a bronchial epithelial cell-derived alarmin implicated in multiple downstream processes involved in asthma pathophysiology.

Eligibility criteria (in addition to criteria for severe asthma): These vary between payers, but usually include severe exacerbations in the last year.

Anti-TSLP may also be considered in patients with no elevated Type 2 markers (Stage 7.1).

Outcomes: In two RCTs in severe asthma patients with severe exacerbations in the last year, anti-TSLP led to 30–70% reduction in severe exacerbations, and improved quality of life, lung function and symptom control, irrespective of allergic status.[89,90] There was a clear correlation between higher baseline blood eosinophils or FeNO and better clinical outcomes.[90] In patients taking maintenance OCS, anti-TSLP did not lead to a reduced OCS dose, compared with placebo.[91]

Potential predictors of good asthma response to anti-TSLP:[92]

- Higher blood eosinophils (strongly predictive)
- Higher FeNO levels (strongly predictive)
- Nasal polyposis.

Additional indications for tezepelumab may include chronic rhinosinusitis with nasal polyps. See Table 1 for doses and age-groups. Check local payer details, as they may differ.

Adverse effects: injection site reactions, anaphylaxis is rare, adverse events generally similar between active and placebo groups. In adults, safety and efficacy of tezepelumab have been reported over up to 2 years of treatment.[93]

Suggested initial trial for severe asthma: at least 4 months

Table 1. Examples of current non-asthma indications for biologic therapy

Biologic	Non-asthma indications include…	Dose and frequency	Ages
Anti-IgE			
Omalizumab and omalizumab-igec	IgE-mediated food allergy	Based on weight and serum IgE	≥1 year
	CRSwNP	Based on weight and serum IgE	≥18 years
	Chronic spontaneous urticaria	150 mg or 300 mg SC every 4 weeks	≥12 years
Anti-IL5/5R			
Mepolizumab	CRSwNP	100 mg SC every 4 weeks	≥18 years
	COPD with eosinophilic phenotype	100 mg SC every 4 weeks	≥18 years
	EGPA	300 mg SC every 4 weeks	≥18 years
	Hypereosinophilic syndrome	300 mg SC every 4 weeks	≥12 years
Depemokimab	CRSwNP	100 mg SC every 26 weeks	≥18 years
Reslizumab	–	–	–
Benralizumab	EGPA	30 mg SC every 4 weeks	≥18 years
Anti-IL4Rα			
Dupilumab*	Moderate-to-severe atopic dermatitis	Adults: 300 mg SC every 2 weeks Children: based on age and weight	≥6 months
	Chronic spontaneous urticaria	Based on age and weight	≥2 years
	CRSwNP	300 mg SC every 2 weeks	≥12 years
	COPD with chronic bronchitis and eosinophilic phenotype	300 mg SC every 2 weeks	≥18 years
	Eosinophilic esophagitis	Based on weight	≥1 year
Anti-TSLP			
Tezepelumab	Chronic rhinosinusitis with nasal polyps	210 mg every 4 weeks	≥12 years

Check local payer details, as they may differ from these. See product information for other indications.

COPD: chronic obstructive pulmonary disease; CRSwNP: chronic rhinosinusitis with nasal polyps; EGPA: eosinophilic granulomatosis with polyangiitis; Ig: immunoglobulin; SC: subcutaneous. *Some indications for dupilumab include a loading dose

→ *Review response to an initial trial of add-on Type 2 targeted therapy*

- At present, there are no well-defined criteria for a good response, but consider exacerbations, symptom control, lung function, treatment intensity (including OCS dose), and patient satisfaction.
- Also consider the patient's biomarkers (interval and during exacerbations, if available), and response of any comorbid Type 2 conditions (atopic dermatitis, nasal polyps, etc). Review response as above.
- If the response is unclear, consider extending the trial to a total of 6–12 months. If there is only a partial response, or a differential response between asthma and comorbid conditions, re-evaluate these diagnoses.
- Monitor for potential adverse events, including for infections.
- If there is no response, stop the biologic therapy, and consider switching to a trial of a different Type 2-targeted therapy, if available and the patient is eligible.

Assess, manage and monitor ongoing severe asthma treatment

9 Review response and implications for treatment

Review response to add-on biologic therapy after 3–4 months, and every 3–6 months for ongoing care, including:

- Asthma: symptom control, both recent e.g., with validated tools such as Asthma Control Test (4 weeks) and Asthma Control Questionnaire (ACQ-5, 1 week), and over the whole period since last review; frequency and severity of exacerbations (including whether OCS were needed); lung function
- Any change in relevant Type 2 comorbidities, e.g., nasal polyps, atopic dermatitis
- Medications: treatment intensity, including courses of OCS and dose of any maintenance OCS, side-effects, affordability
- Patient satisfaction.

The goals of management (GINA 2026 Strategy Report Box 3-3) are to achieve the best possible outcomes for the individual, including long-term symptom control and long-term asthma risk minimization. For patients with a good response to treatment for severe asthma, this may include clinical remission on treatment.

→ *If the patient has had a good response to Type 2 targeted therapy:*

Re-evaluate the need for each asthma medication every 3–6 months, but emphasize to patients and their primary care physician that they should not completely stop ICS-containing therapy. Base the order of reduction or cessation of add-on treatments on potential adverse effects, the observed benefit when the medication was started, patient risk factors, cost, and patient satisfaction. Minimizing the use of OCS is a very high priority.

After reducing/ceasing any medication, confirm asthma stability before making any further treatment changes.

For oral treatments, gradually decrease or stop OCS first, because of their significant adverse effects. Tapering of OCS in severe asthma may be supported by internet-based monitoring of symptom control and FeNO.[94] Monitor patients for risk of adrenal insufficiency by measuring morning serum cortisol, and provide patient and primary care physician with advice about the need for extra corticosteroid doses during injury, illness or surgery for up to 6 months after cessation of long-term OCS. Continue to assess for presence of osteoporosis, and review need for preventative strategies including bisphosphonates.[25]

If asthma remains well controlled, consider reducing or ceasing other therapies, based on the above considerations.

For inhaled treatments, consider ceasing add-on inhaled therapy such as LAMA before reducing ICS-LABA dose. Reduction in dose of ICS-containing therapy may be considered after asthma has been well controlled on biologic therapy for at least 3–6 months and stability has been confirmed after any other medication changes. However, do not completely stop ICS-containing therapy. Previous advice based on consensus was to continue at least medium-dose ICS-LABA. In an open-label study in patients with good symptom control on anti-IL5Rα, most of those randomized to MART with ICS formoterol were able to have their maintenance ICS-formoterol dose gradually reduced (and in some cases stopped, continuing as-needed-only ICS-formoterol) without exacerbations.[95] However, patients who ceased maintenance ICS-formoterol treatment demonstrated evidence of under-dosing with ICS, with reduction in lung function and increase in FeNO, suggesting that in patients with severe asthma, maintenance ICS-containing therapy should not be stopped completely.[95] Any reduction in ICS dose should be considered as a treatment trial and the previous dose reinstated if deterioration occurs (GINA 2026 Strategy Report Box 4-13. Remind patients it is important to continue their maintenance ICS-containing treatment.

For biologic treatments, current consensus advice is that, generally, for a patient with a good response, a trial of withdrawal of the biologic should not be considered until after at least 12 months of treatment, and only if asthma remains well controlled on medium-dose ICS-containing therapy, and (for allergic asthma) there is no further exposure to a

previous well-documented allergic trigger. There are few studies of cessation of biologic therapy,[96-98] in these studies, symptom control worsened and/or exacerbations recurred for many (but not all) patients after cessation of the biologic. For example, in a double-blind RCT, significantly more patients who stopped mepolizumab experienced a severe exacerbation within 12 months than those who continued treatment. In this study, there was a small increase in ACQ-5 but no significant difference in symptom control between groups.[96]

→ *If the patient has NOT had a good response to any Type 2-targeted therapy:*

Stop the biologic therapy

Review the basics for factors contributing to symptoms, exacerbations and poor quality of life (see GINA 2026 Strategy Report Section 2): diagnosis/differential diagnosis, inhaler technique, adherence, modifiable risk factors and triggers including smoking and other environmental exposures at home or work, comorbidities including obesity, medication side-effects or drug interactions, socio-economic and mental health issues.

Consider additional investigations (if not already done): high resolution chest CT, induced sputum to confirm inflammatory phenotype, consider bronchoscopy for alternative or additional diagnoses, consider referral if available, including for diagnosis of alternative conditions.

Reassess treatment options (if not already done), such as:

- Add-on low-dose azithromycin[42,43] (adults only; first check sputum for atypical mycobacteria and check ECG for long QTc (and re-check after a month on treatment); consider potential for antibiotic resistance)
- As last resort, consider add-on low-dose maintenance OCS, but implement strategies such as alternate-day therapy; add bisphosphonates to minimize side-effects on bones,[25] and alert patient to the need for additional corticosteroid therapy during illness or surgery.
- Bronchial thermoplasty can be considered (with registry), but there is limited evidence for safety and efficacy.

Stop ineffective add-on therapies, but do not completely stop ICS.

10 Continue collaborative optimization of patient care

Ongoing management of a patient with severe asthma involves a collaboration between the patient, the primary care physician, specialist(s), and other healthcare providers, to optimize clinical outcomes and patient satisfaction. Continue pharmacologic and non-pharmacologic management to achieve the goal of obtaining the best outcomes for the individual patient.

Continue to review the patient every 3–6 months including:

- Clinical asthma measures (symptom control; exacerbations; lung function)
- Comorbidities
- The patient's risk factors for exacerbations
- Treatments (check inhaler technique and adherence; review need for add-on treatments; assess side-effects including of OCS; optimize comorbidity management and non-pharmacologic strategies)
- The patient's social and emotional needs.

The optimal frequency and location of review (primary care physician or specialist) will depend on the patient's asthma control, risk factors and comorbidities, and their confidence in self-management, and may depend on local payer requirements and availability of specialist physicians.

Communicate regularly with the family physician and other members of the health care team about:

- Outcome of review visits (as above)
- Patient concerns
- Action plan for worsening asthma or other risks
- Changes to medications (asthma and non-asthma); potential side-effects
- Indications and contact details for expedited review.

Overview of asthma medications

For more details about medications, see the full GINA 2026 Strategy Report (**www.ginasthma.org**) and Product Information from manufacturers. Always check local eligibility criteria.

Anti-Inflammatory Reliever Medications

Low-dose combination ICS-formoterol

Medications	Beclometasone-formoterol or budesonide-formoterol
Delivery	pMDI or DPI
Indications	This is the low-dose anti-inflammatory reliever inhaler for adults and adolescents in GINA Track 1, for patients prescribed maintenance-and-reliever therapy (MART) with maintenance ICS-formoterol in Steps 3 5, or for patients prescribed as-needed-only ICS-formoterol in Steps 1 2. In both settings, it reduces the risk of severe exacerbations, compared with using SABA as reliever, with similar symptom control. In adults and adolescents with mild asthma, as needed-only ICS-formoterol reduces emergency visits/hospitalizations by 65%, compared with SABA alone, and by 37% when compared with daily ICS plus as-needed SABA. In children 5–15 years, as-needed-only low-dose budesonide-formoterol reliever reduced exacerbations compared with as-needed SABA. MART with budesonide-formoterol is also recommended for children aged 6–11 in Step 3 or Step 4. See GINA 2026 Strategy Report Box 4-8 for details of medications and doses for AIR-only and MART. Low-dose ICS-formoterol can be taken before exercise to reduce exercise-induced bronchoconstriction, and before or during allergen exposure to reduce allergic responses.
Recommended doses	Most combination ICS-formoterol formulations contain a metered dose of 6 mcg per actuation (delivered dose 4.5 mcg for budesonide-formoterol and 5 mcg for beclometasone-formoterol), together with a low dose of ICS. For adults or adolescents prescribed AIR-only or MART with these formulations, the usual dose is 1 inhalation taken whenever needed for symptom relief. If needed, another inhalation can be taken after a few minutes. Adults and adolescents should be advised to seek medical care if they need more than a total of 12 inhalations of ICS-formoterol in a 24-hour period (maintenance plus reliever doses, delivering a total of 72 mcg [metered dose] of the formoterol component). Since the safety and efficacy of budesonide-formoterol up to this total has been established from large studies (>50,000 patients), GINA suggests that the same advice should also apply for beclometasone-formoterol. For children 6–11 years prescribed AIR-only or MART with budesonide-formoterol, medical care should be sought if they need more than a total of 8 inhalations in a 24-hour period (i.e. delivering a total of 36 mcg (48 mcg metered dose) of the formoterol component). For ICS-formoterol formulations that deliver 2.25 mcg formoterol (metered dose 3 mcg) per actuation, the above numbers of actuations should be doubled. See GINA 2026 Strategy Report Box 4-8 for details of medications and doses for different age-groups.
Adverse effects	As for ICS-formoterol above

Low-dose combination ICS-SABA

Medications	Budesonide-salbutamol (also described as albuterol-budesonide); beclometasone-salbutamol
Delivery	pMDI or DPI
Indications	This is the anti-inflammatory reliever option (instead of SABA) for GINA Track 2. In adults with uncontrolled asthma while using as-needed SABA alone or with low-dose ICS or LTRA, budesonide-salbutamol delivered dose 80/90 mcg (metered dose 100/100 mcg), 2 inhalations taken as needed for symptom relief, reduced the risk of severe exacerbations compared with using a salbutamol reliever, and reduced the need for OCS. In adults with moderate-severe asthma taking maintenance ICS or ICS LABA, budesonide-salbutamol delivered dose 80/90 mcg (metered dose 100/100 mcg), 2 actuations as needed) also reduced the risk of severe exacerbations, compared with SABA reliever; most of the benefit was seen in Step 3. A small number of adolescents was included in both studies. ICS-SABA cannot be used for maintenance-and-reliever therapy. There is no published evidence for as-needed-**only** use of combination budesonide-salbutamol in Track 2 Step 2 compared with daily ICS plus as-needed SABA (or plus as-needed ICS-SABA).
Recommended doses	For combination ICS-SABA formulations delivering 90 mcg salbutamol (100 mcg metered dose), the usual dose is 2 separate inhalations. Patients should be advised to seek medical care if they need more than 6 doses, each of 2 inhalations, in any 24-hour period.
Adverse effects	As for ICS and SABA

Medications for Maintenance Treatment

Inhaled corticosteroids (ICS)

Medications	Beclometasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone, triamcinolone
Delivery	pMDI or DPI
Indications	ICS-containing medications are the most effective anti-inflammatory medications for asthma. ICS reduce symptoms, increase lung function, reduce airway hyperresponsiveness, improve quality of life, and reduce the risk of exacerbations, asthma-related hospitalizations and death. ICS differ in their potency and bioavailability, but most of the benefit is seen at low doses (see GINA 2026 Strategy Report Box 4-2) for low, medium and high doses of different ICS). Adherence with ICS alone is usually very poor because the patient does not perceive any immediate benefit. Preferred delivery of ICS is by dry powder inhaler or, for pMDI, by spacer with mouthpiece, to avoid exposure of the skin and eyes that may occur with spacer and facemask or with nebulized delivery.
Adverse effects	Most patients do not experience side-effects. Local side-effects include oropharyngeal candidiasis and dysphonia; these can be reduced by use of a spacer with pMDIs, and rinsing with water and spitting out after inhalation. Long-term high doses increase the risk of systemic side-effects such as osteoporosis, cataract and glaucoma. Concomitant treatment with cytochrome P450 inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin and clarithromycin may increase the risk of ICS adverse effects such as adrenal suppression.

ICS in combination with a long-acting beta$_2$-agonist bronchodilator (ICS-LABA)

Medications	Beclometasone-formoterol, budesonide-formoterol, fluticasone furoate-vilanterol, fluticasone propionate formoterol, fluticasone propionate-salmeterol, mometasone-formoterol and mometasoneindacaterol
Delivery	pMDI or DPI
Indications	When a low-dose of ICS alone fails to achieve good control of asthma, the addition of LABA to maintenance ICS improves symptoms, lung function and reduces exacerbations in more patients, more rapidly, than doubling the dose of ICS. Two regimens are available for adults and adolescents: low-dose combination beclometasone or budesonide with low-dose formoterol for both maintenance-and-reliever treatment (MART, GINA Track 1), and maintenance ICS-LABA with SABA or ICS-SABA as reliever (Track 2). MART with low-dose ICS-formoterol reliever is preferred as it reduces exacerbations, compared with conventional maintenance therapy with SABA as reliever, and is a simpler regimen. For as-needed-only use of ICS-formoterol in mild asthma, see Anti-inflammatory relievers (below); for ICS-LABA-LAMA see Add-on medications. See GINA 2026 Strategy Report Box 4-2 for low, medium and high doses of ICS in combination with LABA. See GINA 2026 Strategy Report Box 4-8 for medications and doses for anti-inflammatory reliever therapy with ICS-formoterol. Preferred delivery of ICS is by dry powder inhaler or, for pMDI, by spacer with mouthpiece if possible, to avoid exposure of the skin and eyes that may occur with spacer and facemask or with nebulized delivery.
Adverse effects	The LABA component may be associated with tachycardia, headache or cramps. LABA is safe for asthma when used in combination with ICS, but LABA and/or LAMA should not be used without ICS in asthma (or in patients with asthma+COPD) due to increased risk of serious adverse outcomes. Concomitant treatment with cytochrome P450 inhibitors such as ketoconazole, ritonavir, itraconazole, erythromycin and clarithromycin may increase the risk of ICS adverse effects such as adrenal suppression.

Leukotriene receptor antagonists (LTRA) and leukotriene modifiers

Medications	Montelukast, pranlukast, zafirlukast, zileuton
Delivery	Tablets
Indications	Target one part of the inflammatory pathway in asthma. Sometimes used as an option for maintenance therapy, mainly only in children. When used alone: less effective than low-dose ICS. When added to ICS: less effective than ICS-LABA.
Adverse effects	Few in placebo-controlled studies except elevated liver function tests with zileuton and zafirlukast. There are concerns in adults and children about risk of serious behavioral and mood changes, including suicidal ideation, associated with montelukast; this should be discussed with patients/parents/caregivers.

Add-on Maintenance Medications

Long-acting muscarinic antagonists (LAMA) (check your local eligibility criteria)

Medications	Tiotropium, ≥6 years, by mist inhaler, added to separate ICS or ICS-LABA Combination ICS-LABA-LAMA inhalers: For patients aged ≥18 years, beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium and mometasone-indacaterol-glycopyrronium. For patients aged ≥12 years, budesonide-formoterol-glycopyrronium.
Delivery	pMDI or DPI or mist inhaler
Indications	An add-on option using combination or separate inhalers for patients with uncontrolled asthma despite medium- or high-dose ICS-LABA. Modestly improves lung function but not symptoms or quality of life; small reduction in exacerbations. For patients with exacerbations, ensure that ICS is increased to at least medium dose before considering need for add-on LAMA. Note that doses of triple therapy (ICS-LABA-LAMA) for asthma may differ from those approved for COPD.
Adverse effects	Uncommon, but include dry mouth, urinary retention.

Anti-IgE (check your local eligibility criteria)

Medications	Omalizumab or biosimilar (omalizumab-igec), ≥6 years
Indications	Syringe or pen for subcutaneous injection
Use in asthma	An add-on option for patients with severe allergic asthma uncontrolled on high-dose ICS-LABA. May also be indicated for chronic rhinosinusitis with nasal polyps, confirmed IgE-mediated food allergy, and chronic spontaneous (idiopathic) urticaria. See Table 1 for age-groups and doses for these additional indications. Self-administration may be an option.
Adverse effects	Reactions at the site of injection are common but minor. Anaphylaxis is rare.

Anti-IL5 and anti-IL5Rα (check your local eligibility criteria)

Medications	Anti-IL5: mepolizumab (≥6 years, SC injection), depemokimab (≥12 years, SC injection) or reslizumab (≥18 years, intravenous infusion); Anti-IL5 receptor benralizumab (≥12 years, SC injection)
Delivery	Depends on the specific medication, as above
Indications	Add-on options for patients with severe eosinophilic asthma uncontrolled on high-dose ICS-LABA. Maintenance OCS dose can be significantly reduced with benralizumab and mepolizumab. Mepolizumab and benralizumab may also be indicated for eosinophilic granulomatosis with polyangiitis (EGPA), mepolizumab and depemokimab for chronic rhinosinusitis with nasal polyps, and mepolizumab also for hypereosinophilic syndrome and COPD with eosinophilic phenotype; see Table 1 for age-groups and doses for these additional indications. For mepolizumab, benralizumab and depemokimab, self-administration may be an option.
Adverse effects	Headache, and reactions at injection site are common but minor.

Anti-IL4Rα (check your local eligibility criteria)

Medications	Dupilumab (≥6 years)
Delivery	Syringe or pen for subcutaneous injection
Indications	An add-on option for patients with severe eosinophilic or Type 2 asthma uncontrolled on high-dose ICS-LABA, or patients requiring maintenance OCS. Not advised for patients with current or historical blood eosinophils ≥1500/μL. May also be indicated for treatment of other conditions including COPD with chronic bronchitis and elevated blood eosinophils, skin conditions including moderate–severe atopic dermatitis and chronic spontaneous urticaria, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis; see Table 1 for age-groups & doses for these additional indications. Self-administration may be an option.
Adverse effects	Reactions at injection site are common but minor. Transient blood eosinophilia occurs in 4–13% of patients. Rarely, cases of eosinophilic granulomatosis with polyangiitis (EGPA) may be unmasked following reduction/cessation of OCS treatment on dupilumab.

Anti-TSLP (check your local eligibility criteria)

Medications	Tezepelumab, SC injection, ≥12 years
Delivery	Syringe or pen for subcutaneous injection
Indications	An add-on option for patients with severe asthma uncontrolled on high-dose ICS-LABA. In patients taking maintenance OCS, no significant reduction in OCS dose, compared with placebo. May also be indicated for chronic rhinosinusitis with nasal polyps. See Table 1 for age-groups and doses for additional indications.
Adverse effects	Injection-site reactions; anaphylaxis is rare; adverse events generally similar between active and placebo groups.

Systemic corticosteroids

Medications	e.g., prednisone, prednisolone, methylprednisolone, hydrocortisone tablets, dexamethasone
Delivery	Given by tablets or suspension or by IM or IV injection
Indications	Short-term treatment (usually 5–7 days in adults) is important in the treatment of severe acute exacerbations, with main effects seen after 4–6 hours. For severe acute exacerbations, oral corticosteroid (OCS) therapy is preferred to IM or IV therapy and is effective in preventing short-term relapse. Tapering is required if OCS is given for more than 2 weeks. Patients should be reviewed after any exacerbation, to optimize their inhaled treatment to reduce the risk of future exacerbations requiring OCS. As a last resort, long-term treatment with OCS may be required for some patients with severe asthma if biologic therapy is not available, but serious side-effects are problematic. Patients for whom this is considered should be referred for specialist review if available, to have treatment optimized and phenotype assessed.

Adverse effects	Short courses: adverse effects include sepsis, thromboembolism, sleep disturbance, reflux, appetite increase, hyperglycemia, mood changes. Even 4–5 lifetime courses increase cumulative risk of long-term adverse effects e.g., diabetes, osteoporosis, cataract, glaucoma, heart failure. Maintenance use: consider only as last resort, because of significant adverse effects e.g., cataract, glaucoma, hypertension, diabetes, adrenal suppression osteoporosis. Assess for these risks and treat appropriately.

Short-acting bronchodilator reliever medications

Short-acting inhaled beta$_2$ agonist bronchodilators (SABA)

Medications	e.g., salbutamol (albuterol), terbutaline
Delivery	Administered by pMDI, DPI or, rarely, as solution for nebulization or injection
Indications	Inhaled SABAs provide quick relief of asthma symptoms and bronchoconstriction, and for pre-treatment before exercise. SABAs should be used only as-needed (not regularly) and at the lowest dose and frequency required. SABA only treatment is not recommended because of the risk of severe exacerbations and asthma-related death, compared with use of any ICS. Currently, inhaled SABAs are the most commonly used bronchodilator for acute exacerbations requiring urgent primary care visit or ED presentation. Patients should be advised to seek medical care if they need SABA more than 4–6 times in a 24-hour period, or if symptom relief does not last for 4–6 hours. Fenoterol is not recommended because of its association with increased cardiovascular adverse effects and increased risk of asthma mortality. Inhaled epinephrine (adrenaline) is not recommended for treatment of asthma because of the increased risk of systemic adverse effects.
Adverse effects	Tremor and tachycardia are commonly reported with initial use of SABA. Tolerance develops rapidly with even 1–2 weeks of regular use, with increased airway hyperresponsiveness, reduced bronchodilator effect, and increased airway inflammation. Excess use, or poor response indicate poor asthma control and risk of exacerbations. Dispensing of 3 or more 200-dose canisters per year is associated with increased risk of exacerbations, and dispensing of 12 or more canisters per year is associated with markedly increased risk of death.

Short-acting antimuscarinic antagonists (anticholinergics)

Medications	e.g., ipratropium bromide, oxitropium bromide. May be in combination with SABA
Delivery	pMDI or DPI
Indications	As-needed use: ipratropium is a less effective reliever medication than SABA, with slower onset of action. Short-term use in severe acute asthma, where adding ipratropium to SABA in the first 1–2 hours of treatment reduces the risk of hospital admission. Where possible, ipratropium should be delivered by pMDI and spacer with a mouthpiece, to avoid exposure of the eyes which may occur if a spacer with facemask or nebulizer is used.
Adverse effects	Dryness of the mouth or a bitter taste

Acknowledgements

The activities of the Global Initiative of Asthma are supported by the work of members of the GINA Board of Directors and Committees (listed below). GINA collaborated with Tomoko Ichikawa, MS (Institute for Healthcare Delivery Design, University of Illinois at Chicago, USA) and Hugh Musick, MBA (Institute for Healthcare Delivery Design, University of Illinois at Chicago, USA) in developing the first edition of this severe asthma Guide. We thank Alan Kaplan, Ewa Nizankowska-Mogilnicka, Chau Ngo Quy, Ruxandra Ulmeanu, Elisabeth Bel and Sally Wenzel for their valuable input into the first edition of this guide.

GINA publications

Global Strategy for Asthma Management and Prevention (2026). This report provides an integrated approach to asthma that can be adapted for a wide range of health systems. The report has a user-friendly format with many practical summary tables and flow-charts for use in clinical practice. It is updated yearly. Available at **www.ginasthma.org**.

Summary Guide for asthma management and prevention for adults and children older than 5 years (2026). Summary for primary health care providers, to be used in conjunction with the main GINA report. Available at **www.ginasthma.org**.

What's new in 2026? slide set. Available at **www.ginasthma.org**.

GINA 2026 Difficult-To-Treat and Severe Asthma slide set. Available at **www.ginasthma.org**.

Other resources for severe asthma

Severe asthma toolkit – Australian Centre of Excellence in Severe Asthma https://toolkit.severeasthma.org.au

References

1. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.

2. Hekking P, Wener R, Amelink M, et al. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015; 135: 896-902.

3. Lefebvre P, Duh MS, Lafeuille M-H, et al. Acute and chronic systemic corticosteroid–related complications in patients with severe asthma. J Allergy Clin Immunol 2015; 136: 1488-1495.

4. Chalitsios CV, McKeever TM, Shaw DE. Incidence of osteoporosis and fragility fractures in asthma: a UK population-based matched cohort study. Eur Respir J 2021; 57: 2001251.

5. Foster JM, McDonald VM, Guo M, et al. "I have lost in every facet of my life": the hidden burden of severe asthma. Eur Respir J 2017; 50: 1700765.

6. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. BMJ 2017; 357: j1415.

7. Ross KR, Gupta R, DeBoer MD, et al. Severe asthma during childhood and adolescence: A longitudinal study. J Allergy Clin Immunol 2020; 145: 140-146 e149.

8. O'Neill S, Sweeney J, Patterson CC, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax 2015; 70: 376-378.

9. Sadatsafavi M, Lynd L, Marra C, et al. Direct health care costs associated with asthma in British Columbia. Can Respir J 2010; 17: 74-80.

10. Hashimoto S, Bel EH. Current treatment of severe asthma. Clin Exp Allergy 2012; 42: 693-705.

11. Hallstrand TS, Leuppi JD, Joos G, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J 2018; 52: 1801033.

12. McNicholl DM, Stevenson M, McGarvey LP, et al. The utility of fractional exhaled nitric oxide suppression in the identification of nonadherence in difficult asthma. Am J Respir Crit Care Med 2012; 186: 1102-1108.

13. Heaney LG, Busby J, Bradding P, et al. Remotely monitored therapy and nitric oxide suppression identifies nonadherence in severe asthma. Am J Respir Crit Care Med 2019; 199: 454-464.

14. Hale EM, Greene G, Mulvey C, et al. Use of digital measurement of medication adherence and lung function to guide the management of uncontrolled asthma (INCA Sun): a multicentre, single-blinded, randomised clinical trial. Lancet Respir Med 2023; 11: 591-601.

15. Cockcroft DW. Clinical concerns with inhaled beta2-agonists: adult asthma. Clin Rev Allergy Immunol 2006; 31: 197-208.

16. Stanford RH, Shah MB, D'Souza AO, et al. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol 2012; 109: 403-407.

17. Nwaru BI, Ekstrom M, Hasvold P, et al. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J 2020; 55: 1901872.

18. Suissa S, Ernst P, Boivin JF, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med 1994; 149: 604-610.

19. Paris J, Peterson EL, Wells K, et al. Relationship between recent short-acting beta-agonist use and subsequent asthma exacerbations. Ann Allergy Asthma Immunol 2008; 101: 482-487.

20. Basheti IA, Armour CL, Bosnic-Anticevich SZ, et al. Evaluation of a novel educational strategy, including inhaler-based reminder labels, to improve asthma inhaler technique Patient Educ Couns 2008; 72: 26-33.

21. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. Cochrane Database Syst Rev 2017; 4: CD012226.

22. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller an quick relief therapy with exacerbations and symptom control in persistent asthma: A systematic review and meta-analysis. JAMA 2018; 319: 1485-1496.

23. McLoughlin RF, Clark VL, Urroz PD, et al. Increasing physical activity in severe asthma: a systematic review and meta-analysis. Eur Respir J 2022; 60: 2200546.

24. U.S. Food and Drug Administration. FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis. 3-4-2020 FDA Drug Safety Communication. FDA; 2020 [updated 13 March 2020; cited 2026 May]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug.

25. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of gluco corticoid-induced osteoporosis. Arthritis Care Res (Hoboken) 2017; 69: 1095-1110.

26. Centers for Disease Control and Prevention. Clinical Overview of Strongyloides. [web page]: U.S. Department of Health & Human Services; 2018 [updated 11 February 2026; cited 2026 May]. Available from: https://www.cdc.gov/strongyloides/hcp/clinical-overview/index.html

27. Clark VL, Gibson PG, Genn G, et al. Multidimensional assessment of severe asthma: A systematic review and meta-analysis. Respirology 2017; 22: 1262-1275.

28. Brown T, Jones T, Gove K, et al. Randomised controlled trials in severe asthma: selection by phenotype or stereotype. Eur Respir J 2018; 52: 1801444.

29. Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. N Engl J Med 2017; 377: 965-976.

30. Bleecker ER, Meyers DA, Billheimer D, et al. Clinical implications of longitudinal blood eosinophil counts in patients with severe asthma. J Allergy Clin Immunol Pract 2023; 11: 1805-1813.

31. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy 2018; 11: 193-204.

32. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. Lancet Respir Med 2021; 9: 1165-1173.

33. Meulmeester FL, Mailhot-Larouche S, Celis-Preciado C, et al. Inflammatory and clinical risk factors for asthma attacks (ORACLE2): a patient-level meta-analysis of control groups of 22 randomised trials. Lancet Respir Med 2025; Online ahead of print: DOI 10.1016/s2213-2600(1025)00037-00032.

34. Hartl S, Breyer MK, Burghuber OC, et al. Blood eosinophil count in the general population: typical values and potential confounders. Eur Respir J 2020; 55: 1901874.

35. Amaral R, Jacinto T, Malinovschi A, et al. The influence of individual characteristics and non-respiratory diseases on blood eosinophil count. Clin Transl Allergy 2021; 11: e12036.

36. Högman M, Bowerman C, Chavez L, et al. ERS technical standard: Global Lung Function Initiative reference values for exhaled nitric oxide fraction (FENO50). Eur Respir J 2024; 63: 2300370.

37. Lugogo NL, Kreindler JL, Martin UJ, et al. Blood eosinophil count group shifts and kinetics in severe eosinophilic asthma. Ann Allergy Asthma Immunol 2020; 125: 171-176.

38. Biener L, Milger K, Suhling H, et al. Impact of short-term pausing of oral corticosteroids on blood eosinophil count in patients with severe asthma. Pneumologie 2023; 77: 357-362.

39. Sobieraj DM, Baker WL, Nguyen E, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis. JAMA 2018; 319: 1473-1484.

40. Kim LH, Saleh C, Whalen-Browne A, et al. Triple vs dual inhaler therapy and asthma outcomes in moderate to severe asthma: a systematic review and meta-analysis. JAMA 2021; 325: 2466-2479.

41. Oba Y, Anwer S, Maduke T, et al. Effectiveness and tolerability of dual and triple combination inhaler therapies compared with each other and varying doses of inhaled corticosteroids in adolescents and adults with asthma: a systematic review and network meta-analysis. Cochrane Database Syst Rev 2022; 12: CD013799.

42. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. Lancet 2017; 390: 659-668.

43. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013; 68: 322-329.

44. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med 2010; 181: 116-124.

45. Chaudhuri R, Rubin A, Sumino K, et al. Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials. Lancet Respir Med 2021; 9: 457-466.

46. Gamble J, Stevenson M, McClean E, et al. The prevalence of nonadherence in difficult asthma. Am J Respir Crit Care Med 2009; 180: 817-822.

47. Chan AH, Harrison J, Black PN, et al. Using electronic monitoring devices to measure inhaler adherence: a practical guide for clinicians. J Allergy Clin Immunol Pract 2015; 3: 335-349.e331-335.

48. Agache I, Rocha C, Beltran J, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma. Allergy 2020; 75: 1043-1057.

49. Bousquet J, Humbert M, Gibson PG, et al. Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies. J Allergy Clin Immunol Pract 2021; 9: 2702-2714.

50. Namazy J, Cabana MD, Scheuerle AE, et al. The Xolair Pregnancy Registry (EXPECT): the safety of omalizumab use during pregnancy. J Allergy Clin Immunol 2015; 135: 407-412.

51. Brusselle G, Michils A, Louis R, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: The PERSIST study. Respir Med 2009; 103: 1633-1642.

52. Humbert M, Taille C, Mala L, et al. Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study. Eur Respir J 2018; 51: 1702523.

53. Busse WW. Are peripheral blood eosinophil counts a guideline for omalizumab treatment? STELLAIR says no! Eur Respir J 2018; 51: 1800730.

54. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. J Allergy Clin Immunol Pract 2019; 7: 156-164 e151.

55. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol 2020; 146: 595-605.

56. Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev 2014; 1: CD003559.

57. Zazzali JL, Raimundo KP, Trzaskoma B, et al. Changes in asthma control, work productivity, and impairment with omalizumab: 5-year EXCELS study results. Allergy Asthma Proc 2015; 36: 283-292.

58. Agache I, Beltran J, Akdis C, et al. Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab) for severe eosinophilic asthma. A systematic review for the EAACI Guidelines - recommendations on the use of biologicals in severe asthma. Allergy 2020; 75: 1023-1042.

59. Jackson DJ, Wechsler ME, Jackson DJ, et al. Twice-yearly depemokimab in severe asthma with an eosinophilic phenotype. N Engl J Med 2024; 391: 2337-2349.

60. Farne HA, Wilson A, Milan S, et al. Anti-IL-5 therapies for asthma. Cochrane Database Syst Rev 2022; 7: CD010834.

61. Lemiere C, Taillé C, Lee JK, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two Phase III trials. Respir Res 2021; 22: 184.

62. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med 2018; 6: 51-64.

63. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. Lancet 2000; 356: 2144-2148.

64. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014; 371: 1189-1197.

65. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med 2017; 376: 2448-2458.

66. Jackson DJ, Bacharier LB, Gergen PJ, et al. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet 2022; 400: 502-511.

67. Chupp G, Nagase H, Skowasch D, et al. Switching to twice-yearly depemokimab from mepolizumab/benralizumab in severe asthma: A multicenter, randomized, double-blind, Phase 3A Clinical Trial (NIMBLE). Am J Respir Crit Care Med 2026; Online ahead of print 11 Feb.

68. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. The Lancet Respiratory medicine 2016; 4: 549-556.

69. Brusselle G, Germinaro M, Weiss S, et al. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther 2017; 43: 39-45.

70. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018; 52: 1800936.

71. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011; 128: 989-995.e988.

72. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial. J Allergy Clin Immunol 2017; 140: 1024-1031.e1014.

73. Gevaert P, Desrosiers M, Cornet M, et al. Efficacy and safety of twice per year depemokimab in chronic rhinosinusitis with nasal polyps (ANCHOR-1 and ANCHOR-2): phase 3, randomised, double-blind, parallel trials. Lancet 2025; 405: 911-926.

74. Canonica GW, Harrison TW, Chanez P, et al. Benralizumab improves symptoms of patients with severe, eosinophilic asthma with diagnosis of nasal polyposis. Allergy 2022; 77: 150-161.

75. Korn S, Bourdin A, Chupp G, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. J Allergy Clin Immunol Pract 2021; 9: 4381-4392.e4384.

76. Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol 2019; 143: 1742-1751.e1747.

77. Agache I, Song Y, Rocha C, et al. Efficacy and safety of treatment with dupilumab for severe asthma: A systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma. Allergy 2020; 75: 1058-1068.

78. Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. J Allergy Clin Immunol Pract 2020; 8: 516-526.

79. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018; 378: 2475-2485.

80. Sher LD, Wechsler ME, Rabe KF, et al. Dupilumab reduces oral corticosteroid use in patients with corticosteroid-dependent severe asthma: an analysis of the phase 3, open-label extension TRAVERSE trial. Chest 2022; 162: 46-55.

81. Bacharier LB, Maspero JF, Katelaris CH, et al. Dupilumab in children with uncontrolled moderate-to-severe asthma. N Engl J Med 2021; 385: 2230-2240.

82. Bacharier LB, Maspero JF, Katelaris CH, et al. Assessment of long-term safety and efficacy of dupilumab in children with asthma (LIBERTY ASTHMA EXCURSION): an open-label extension study. Lancet Respir Med 2024; 12: 45-54.

83. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018; 378: 2486-2496.

84. Bacharier LB, Pavord ID, Maspero JF, et al. Blood eosinophils and fractional exhaled nitric oxide are prognostic and predictive biomarkers in childhood asthma. J Allergy Clin Immunol 2024; 154: 101-110.

85. Busse WW, Kraft M, Domingo C, et al. Impact of asthma age of onset or duration on efficacy of dupilumab in moderate-to-severe type 2 asthma. J Asthma 2025; 62: 1678-1689.

86. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394: 1638-1650.

87. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: A randomized clinical trial. JAMA 2016; 315: 469-479.

88. Maspero JF, Peters AT, Chapman KR, et al. Long-term safety of dupilumab in patients With moderate-to-severe asthma: TRAVERSE continuation study. J Allergy Clin Immunol Pract 2024; 12: 991-997.e996.

89. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med 2017; 377: 936-946.

90. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med 2021; 384: 1800-1809.

91. Wechsler ME, Menzies-Gow A, Brightling CE, et al. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. Lancet Respir Med 2022; 10: 650-660.

92. Corren J, Menzies-Gow A, Chupp G, et al. Efficacy of tezepelumab in severe, uncontrolled asthma: pooled analysis of the PATHWAY and NAVIGATOR clinical trials. Am J Respir Crit Care Med 2023; 208: 13-24.

93. Menzies-Gow A, Wechsler ME, Brightling CE, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. Lancet Respir Med 2023; 11: 425-438.

94. Hashimoto S, Brinke AT, Roldaan AC, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic andomised controlled trial. Thorax 2011; 66: 514-520.

95. Jackson DJ, Heaney LG, Humbert M, et al. Reduction of daily maintenance inhaled corticosteroids in patients with severe eosinophilic asthma treated with benralizumab (SHAMAL): a randomised, multicentre, open-label, phase 4 study. Lancet 2024; 403: 271-281.

96. Haldar P, Brightling CE, Singapuri A, et al. Outcomes after cessation of mepolizumab therapy in severe eosinophilic asthma: a 12-month follow-up analysis. J Allergy Clin Immunol 2014; 133: 921-923.

97. Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. J Allergy Clin Immunol 2017; 140: 162-169.e162.

98. Brightling CE, Caminati M, Llanos JP, et al. Biomarkers and clinical outcomes after tezepelumab cessation: Extended follow-up from the 2-year DESTINATION study. Ann Allergy Asthma Immunol 2024; 133: 310-317.e314.

99. Moore WC, Kornmann O, Humbert M, et al. Stopping versus continuing long-term mepolizumab treatment in severe eosinophilic asthma (COMET study). Eur Respir J 2022; 59: 2100396.

Visit the GINA website at www.ginasthma.org