GLOBAL INITIATIVE FOR ASTHMA

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A Short GINA Guide for Health Professionals

V4.0 August 2023

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

© Global Initiative for Asthma, 2023 www.ginasthma.org

GLOBAL INITIATIVE FOR ASTHMA

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A Short GINA Guide for Health Professionals

V4.0 August 2023

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Suggested citation: Global Initiative for Asthma. Difficult-To-Treat & Severe Asthma in Adolescent and Adult Patients, 2023. Available from: www.ginasthma.org

Symbols and abbreviations

*	Check local eligibility criteria as these may vary from those listed
+, ++, +++	Plus signs indicate the strength of an association
~	Approximately
ACE	Angiotensin-converting enzyme
ACQ-5	5-item Asthma Control Questionnaire
ABPA	Allergic bronchopulmonary aspergillosis
AERD	Aspirin-exacerbated respiratory disease
ANCA	Antineutrophil cytoplasmic antibody
BNP	B-type natriuretic peptide
CBC	Complete blood count (also known as FBC, full blood count)
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT/HRCT	Computerized tomography/high resolution computerized tomography
CXR	Chest X-ray
DEXA	Dual-energy X-ray absorptiometry
DPI	Dry powder inhaler
DLCO	Diffusing capacity in the lung for carbon monoxide
ED	Emergency department
EGPA	Eosinophilic granulomatosis with polyangiitis
FeNO	Fraction of exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastro-esophageal reflux disease
GP	General practitioner; primary care physician
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IV	Intravenous
LABA	Long-acting $beta_2$ agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist (also called leukotriene modifier)
NSAID	Nonsteroidal anti-inflammatory drug
OCS	Oral corticosteroids
OSA	Obstructive sleep apnea
pMDI	Pressurized metered dose inhaler
QTc	Corrected QT interval from electrocardiogram
RCT	Randomized controlled trial
SABA	Short-acting $beta_2$ agonists
SC	Subcutaneous
TSLP	Thymic stromal lymphopoietin
VCD	Vocal cord dysfunction (now part of inducible laryngeal obstruction)

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVES - FOR REFERENCE ONLY

Table of Contents

Symbols and abbreviations 2
Goal of this guide 4
How to use this guide 5
Definitions: uncontrolled, difficult-to-treat and severe asthma 6
Prevalence: how many people have severe asthma? 6
Importance: the impact of severe asthma 7
Severe asthma decision tree: diagnosis and management 8

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

GP OR SPECIALIST CARE

		Decision Tree	*Detail Pages*
1	Confirm the diagnosis (asthma or differential diagnoses)	8	12
2	Look for factors contributing to symptoms, exacerbations and poor quality of life	8	13
3	Review and optimize management	8	13
4	Review response after approximately 3-6 months	8	14

Assess and treat severe asthma phenotypes

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

		Decision Tree	*Detail Pages*
5	Investigate further and provide patient support	9	15
6	Assess the severe asthma phenotype	9	16
7.1	Consider other treatments if there is NO evidence of Type 2 inflammation	9	17
7.2	Consider non-biologic treatments if there IS evidence of Type 2 airway inflammation	9	17
7.3	Is Type 2-targeted biologic therapy available and affordable?	9	18
8	Consider add-on biologic Type 2-targeted treatments	10	18

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Manage and monitor severe asthma treatment

SPECIALIST AND PRIMARY CARE IN COLLABORATION

		Decision Tree	*Detail Pages*
9	Review response and implications for treatment	11	22
10	Continue collaborative optimization of patient care	11	23

Glossary of asthma medication classes 24
Acknowledgements 29
GINA publications 29
Other resources for severe asthma 29
References 30

Goal of this Guide

The goal of this guide is to provide health professionals with a practical summary of 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. More details on asthma management in clinical practice, particularly for primary care, can be found in the GINA 2023 Strategy Report, available from www.ginasthma.org.

How was the Guide developed?

The recommendations in this guide were based on the most reliable sources available for each topic: evidence from good-quality systematic reviews or randomized controlled trials (RCTs), robust observational data if no controlled trials available, or expert consensus by experienced clinicians and researchers where no published evidence available. Development of the Guide and decision tree included extensive collaboration with experts in human-centered design to enhance the utility of these resources for end-users. This means translating existing high-level flowcharts and text-based information to a more detailed visual format, and applying information architecture and diagramming principles.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED FOR REFERENCE ONLY

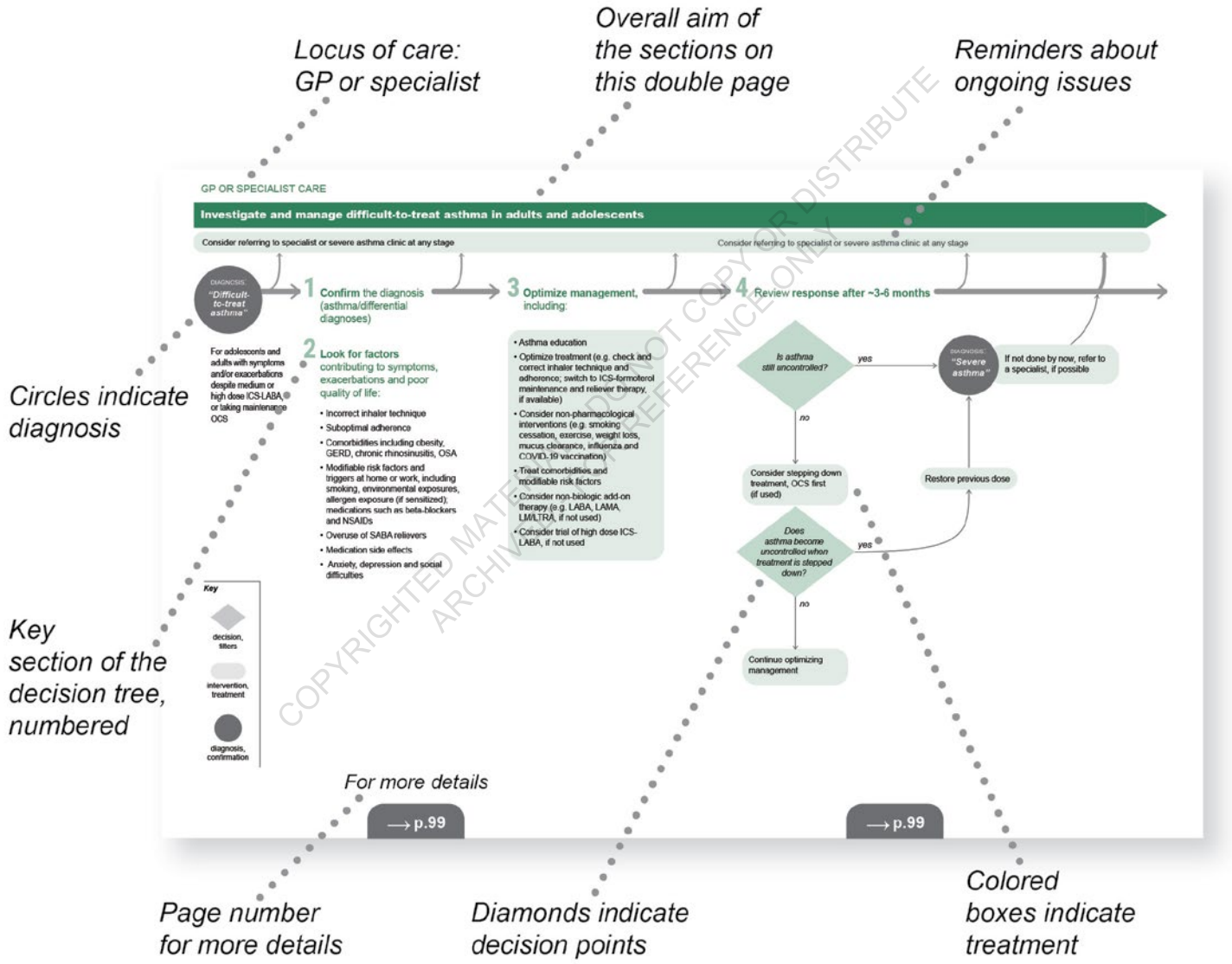
This **GINA Guide** *is intended as a practical guide for health professionals on the assessment and management of difficult-to-treat and severe asthma. It does NOT contain all of the information required for managing asthma. The Guide should be used in conjunction with the full GINA 2023 Strategy Report. Health professionals should also use their own clinical judgment and take into account any local restrictions or payer requirements. GINA cannot be held liable or responsible for inappropriate healthcare associated with the use of this document, including any use which is not in accordance with applicable local or national regulations or guidelines.*

How to use this Guide

The table of contents (page 3) summarizes the overall steps involved in assessing and treating an adult or adolescent who presents with difficult-to-treat asthma (see definitions on page 6).

A clinical decision tree is found on pages 8 to 15, providing brief information about what should be considered in each phase. The decision tree is divided into three broad areas:

- **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, GP, specialist and other health professionals.



COPYRIGHTED MATERIAL – DO NOT COPY OR DISTRIBUTE
ARCHIVE COPY FOR REFERENCE ONLY

More detailed information about each of the numbered sections of the decision tree follows, starting on page 16. GINA 2023 Box numbers refer to Global Strategy for Asthma Management and Prevention, 2023 (the Strategy Report), available at www.ginasthma.org.

Key references and additional resources are found at the end of the guide, starting on page 31.

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[1] 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, asthma may appear to be difficult to treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking or comorbidities, or because the diagnosis is incorrect.

Severe asthma[1] is a subset of difficult-to-treat asthma (Box 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.

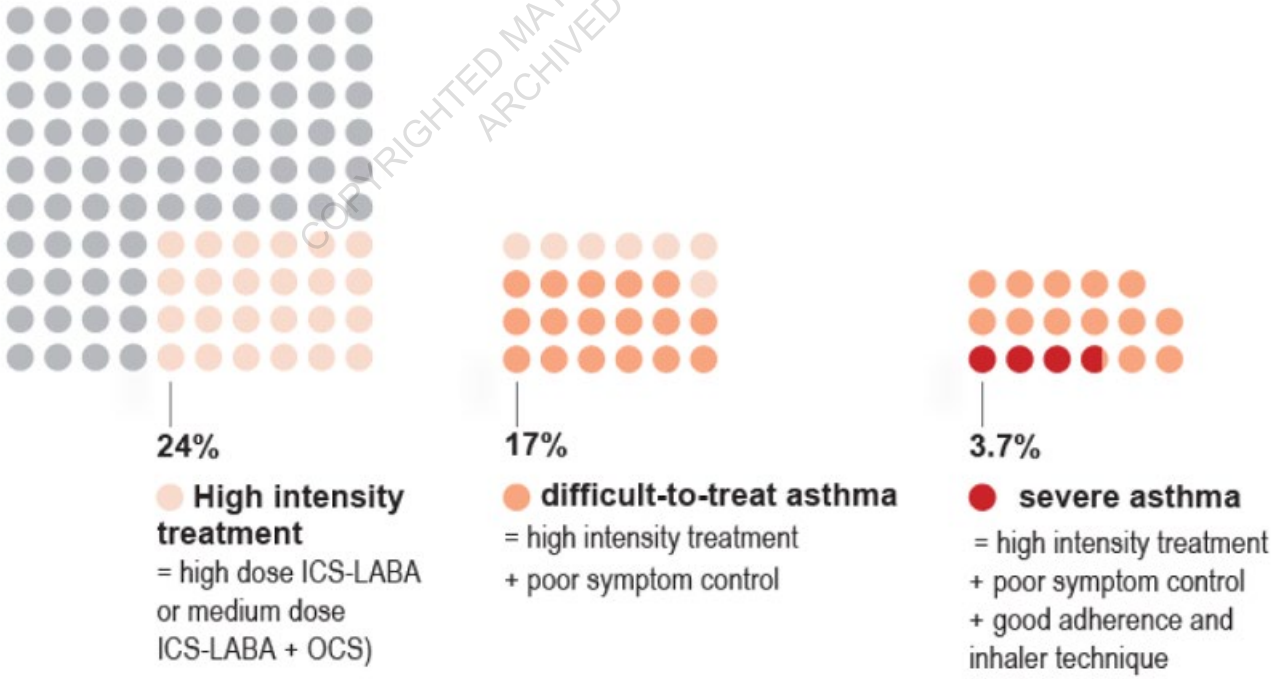
Asthma is not classified as severe if it markedly improves when contributory factors such as inhaler technique and adherence are addressed.[1]

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 (Box 1).[2]

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Box 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]

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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 ~30% of male and female adolescents; the only predictor of asthma becoming non-severe was 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 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.

GP OR SPECIALIST CARE

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

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: ***"Difficult-to-treat asthma"***

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 **Confirm** the diagnosis (asthma/differential diagnoses)

2 **Look for factors** contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 **Optimize management,** including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review **response after ~3-6 months**

Is asthma still uncontrolled?

yes → DIAGNOSIS: ***"Severe asthma"*** → If not done by now, refer to a specialist, if possible

no → Consider stepping down treatment, OCS first (if used)

Does asthma become uncontrolled when treatment is stepped down?

yes → Restore previous dose

no → Continue optimizing management

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Key

- decision, filters
- intervention, treatment
- diagnosis, confirmation

For more details

→ pg 12 → pg 13 → pg 14

© GINA 2023

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 ***Investigate*** further and provide ***patient support***

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the ***severe asthma phenotype***

Could patient have Type 2 airway inflammation?

yes

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

no

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4Rα* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Not currently eligible for T2-targeted biologic therapy

Go to section **10**

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

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

For more details

→ pg 15 → pg 16 → pg 17

© GINA 2023

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

8 Consider *add-on biologic Type 2-targeted* treatments

- Consider add-on Type 2-targeted biologic therapy for patients with exacerbations or poor symptom control on high dose ICS-LABA, who have evidence of Type 2 inflammation*
- Consider **local payer eligibility criteria***, **comorbidities** and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Eligibility

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**

- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

no / no

Anti-IL5 / Anti-IL5R *(benralizumab, mepolizumab, reslizumab)*

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**

- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

no / no

Anti-IL4Rα *(dupilumab)*

*Is the patient eligible for **anti-IL4R**α for severe eosinophilic/Type 2 asthma?**

- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

no / no

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**

- Exacerbations in last year

Eligible for none? Return to section **7**

Predictors of asthma response

What factors may predict good asthma response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

What factors may predict good asthma response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

What factors may predict good asthma response to anti-IL4Rα?

- Higher blood eosinophils +++
- Higher FeNO +++

What factors may predict good asthma response to anti-TSLP?

- Higher blood eosinophils +++
- Higher FeNO +++

Choose one if eligible*; trial for at least 4 months and assess response

*Good asthma response?** — *yes* → Good response to T2-targeted therapy

unclear → Extend trial to 6-12 months*

no → **STOP add-on**

Consider switching to a different Type 2-targeted therapy, if eligible*

no → Little/no response to T2-targeted therapy

No evidence of Type 2 airway inflammation

No evidence of Type 2 airway inflammation. Go to section **10**

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

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

For more details

→ **pg 18**

© GINA 2023

Monitor / Manage severe asthma treatment

Continue to optimize management

9 Review **response**

- Asthma: symptom control, exacerbations, lung function
- Type 2 comorbidities e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, side-effects, affordability
- Patient satisfaction

yes

If good response to Type 2-targeted therapy

- Re-evaluate the patient every 3-6 months*
- For **oral treatments:** consider decreasing/stopping OCS first (and check for adrenal insufficiency), then stopping other add-on medication
- For **inhaled treatments:** consider decreasing after 3-6 months; continue at least moderate dose ICS-LABA
- Re-evaluate need for ongoing biologic therapy
- Order of reduction of treatments based on observed benefit, potential side-effects, cost and patient preference

no

If no good response to Type 2-targeted therapy

- Stop the biologic therapy
- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects, emotional support
- Consider high resolution chest CT (if not done)
- Reassess phenotype and treatment options
  - Induced sputum (if available)
  - Consider add-on low dose azithromycin
  - Consider bronchoscopy for alternative/additional diagnoses
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies
- Do not stop ICS

No evidence of Type 2 airway inflammation. Go to section **10**

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

For more details

→ **pg 22**

10 Continue to **optimize management** as in section **3**, including:

- Inhaler technique
- Adherence
- Comorbidity management
- Non-pharmacologic strategies
- Patients' social/emotional needs
- Two-way communication with GP for ongoing care

Notes:

→ **pg 23**

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

© GINA 2023

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

Care by **GP or SPECIALIST**

1 Confirm the diagnosis (asthma or differential diagnoses)

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
- The patient has food allergy or 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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, ACE inhibitors
- **Wheeze:** obesity, COPD, tracheobronchomalacia, VCD.

Investigate according to clinical suspicion and age (see GINA 2023 Box 1-5).[10]

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.[11]

Perform spirometry, before and after bronchodilator, to assess baseline lung function and seek objective evidence of variable expiratory airflow limitation. 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 2023 Box 1-3).[10] Check full flow-volume curve to assess for upper airway obstruction. If spirometry is normal or is not available, provide the patient with a peak flow meter and diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (SABA for at least 6 hours, LABA for up to 2 days depending on duration of action).[12]

See GINA 2023 (Chapter 1)[10] for details about diagnostic testing, including strategies for confirming the diagnosis of asthma in patients already taking ICS-containing treatment.

Airflow limitation may be persistent in patients with long-standing 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, exacerbations and poor quality of life

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 2023 Box 3-23).[9] 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. Electronic inhaler monitoring, if available, can be helpful in screening for poor adherence.
- **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.
- **Modifiable risk factors and triggers:** identify factors that increase the risk of exacerbations, e.g. smoking, 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 nonsteroidal anti-inflammatory drugs (NSAIDs). For allergens, check for sensitization using skin prick testing or specific IgE.
- **Regular or over-use of SABAs** causes beta-receptor down-regulation and reduction in response,[13] leading in turn to greater use. Overuse may also be habitual. Dispensing of ≥3 SABA canisters per year (average use more than daily) is associated with increased risk of emergency department visit or hospitalization independent of severity,[14,15] and dispensing of ≥12 canisters per year (one a month) with substantially increased risk of death.[15,16] Risks are higher with nebulized SABA.[17]
- **Anxiety, depression and social and economic problems:** these are very common in patients with difficult-to-treat 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 thrush 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.

COPYRIGHTED MATERIAL. DO NOT COPY OR DISTRIBUTE. ARCHIVED FOR REFERENCE ONLY

3 Review and optimize management

Review and optimize treatment for asthma, and for comorbidities and risk factors identified in Section 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 inhaled controller 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.[18] Address suboptimal adherence, both intentional and unintentional.[19] Switch to ICS-formoterol maintenance and reliever regimen if available, to reduce the risk of exacerbations.[20]
- **Consider non-pharmacologic add-on therapy**, e.g. smoking cessation, physical exercise,[21] healthy diet, weight loss, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance, if feasible, for patients who are sensitized and exposed (see GINA 2023 Box 3-18).[10]

- **Treat comorbidities and modifiable risk factors** identified in Section 2, where there is evidence for benefit; however, there is no evidence to support routine treatment of asymptomatic GERD. Avoid medications that make asthma worse (e.g. 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 trial of non-biologic medication** added to medium/high dose ICS, e.g., LABA, LAMA, LTRA if not already tried. Note FDA boxed warning about potential neuropsychiatric effects with LTRAs.[22]
- **Consider 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, 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED FOR REFERENCE ONLY

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

YES: if asthma is still uncontrolled, the diagnosis of severe asthma has been confirmed. 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 remove other add-on therapy, then decrease ICS dose, but do not stop ICS. See GINA 2023 (Box 3-16)[10] 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 has been confirmed. 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.

Care by **SPECIALIST, in SEVERE ASTHMA CLINIC IF AVAILABLE**

5 Investigate further and provide patient support

Further assessment and management should be by a specialist, preferably in a multidisciplinary severe asthma clinic if available. The team may include a certified asthma educator and health professionals from fields such as speech pathology, ear nose and throat (ENT), 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:

- Blood tests: complete blood count, CRP, IgG, IgA, IgM, IgE, fungal precipitins including Aspergillus
- Allergy testing for clinically relevant allergens: skin prick test or specific IgE, if not already done
- Other pulmonary investigations: DLCO; CXR or high-resolution chest CT
- Bone density scan, because of risk of osteoporosis with maintenance or frequent OCS or long-term high dose ICS.[23]

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. Strongyloides infection is usually asymptomatic.[24]

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

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 the identification of comorbidities, and improves outcomes.[25]

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.[26]

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

6 Assess the severe asthma phenotype

The next step is to assess the patient's inflammatory phenotype – is it Type 2 high or low?

What is Type 2 inflammation?

Type 2 inflammation is found in the majority of people with severe asthma. It is characterized by cytokines such as interleukin (IL)-4, IL-5 and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It may also be activated by viruses, bacteria and irritants that stimulate the innate immune system via production of IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) by epithelial cells. Type 2 inflammation is often characterized by elevated eosinophils or increased FeNO, and may be accompanied by atopy, whereas non-Type 2 inflammation is often characterized by increased neutrophils.[27]

In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. It may respond to OCS but their serious adverse effects[3,28] mean that alternative treatments should be sought.

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.[29]

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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, and/or
- FeNO ≥20ppb, and/or
- Sputum eosinophils ≥2%, and/or
- 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.

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 section 8 and local criteria.

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 asthma is non-Type 2. 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.[30]

Why is the inflammatory phenotype assessed on high dose ICS?

- Most 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 (as in section 6):

- Review the basics for factors that may be contributing to symptoms or exacerbations: differential diagnosis, inhaler technique, adherence, comorbidities, medication side-effects (Section 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 as separate inhaler or triple combination therapy[31]
    - Low-dose azithromycin (adults)[32,33] 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 section 8 for more details)
    - Anti-TSLP thymic stromal lymphopoietin) (but insufficient evidence in patients taking maintenance OCS; see section 8 for more details)
    - As a last resort, consider add-on low dose OCS, but implement strategies such as alternate-day treatment to minimize side-effects.
- Consider bronchial thermoplasty, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.[34,35] For more details, see 2023 GINA report page 87.
- Stop ineffective add-on therapies.
- Continue to optimize treatment, including inhaler technique, adherence, non-pharmacologic strategies and treating comorbidities (see sections 3 and 10).

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

7.2 Consider non-biologic treatments if there IS evidence of Type 2 airway inflammation

For patients with elevated Type 2 biomarkers despite high dose ICS (see section 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,[36] or electronic inhaler monitoring.[37] In one study, suppression of high FeNO after 5 days of directly observed therapy was an indicator of past poor adherence.[38]
- **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 2023 Strategy Report, Chapter 3.4).[10] For example, for aspirin-exacerbated respiratory disease (AERD), consider add-on LTRA and possibly aspirin desensitization. For allergic bronchopulmonary aspergillosis (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.

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 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 sections 3 and 10).

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 biomarkers or need maintenance OCS. Where relevant, test for parasitic infection, and treat if present, before commencing treatment (see section 5).

Consider whether to start first with anti-IgE, anti-IL5/5R, anti-IL4R 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 polyposis
- Predictors of asthma response (see below)
- Cost
- Dosing frequency
- Delivery route (IV or SC; potential for self-administration)
- Patient preference.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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. GINA suggests that the first dose of asthma biologic therapy should not be given on the same day as a COVID-19 vaccine, so that adverse effects of either can be more easily distinguished.

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 may include: omalizumab for ages ≥6 years, given by SC injection every 2–4 weeks, with dose based on weight and serum IgE. May also be indicated for nasal polyps and chronic spontaneous (idiopathic) urticaria. Self-administration may be an option. Check local regulatory and 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) vary between payers, but usually include:

- Sensitization to inhaled allergen(s) on skin prick testing or specific IgE, and
- 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: 44% decrease in severe exacerbations; improved quality of life.[39] No double-blind randomized controlled trials 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.[40] In patients with nasal polyps, omalizumab improved subjective and objective outcomes.[41] See GINA 2023 (Chapter 3.4)[10] for additional details about treatment of chronic rhinosinusitis with nasal polyps (CRSwNP). A registry study of omalizumab in pregnancy found no increased risk of congenital malformations.[42]

Potential predictors of good asthma response to omalizumab:

- Baseline IgE level does not predict likelihood of response[43]
- In a post-hoc analysis of one clinical trial, a greater decrease in exacerbations was observed (cf. placebo) with blood eosinophils ≥260/μL[44,45] or FeNO ≥19.5 ppb[44] (these criteria representing their median value in that study) but in two large observational studies, exacerbations were reduced with both low or high blood eosinophils[46-48] or with both low or high FeNO.[48]
- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms.

Adverse effects: injection site reactions; anaphylaxis in ~0.2% patients[49]

Suggested initial trial: at least 4 months

⟶ *Add-on anti-IL5 or anti-IL5R for severe eosinophilic asthma*

Regulatory approvals 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. 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. Mepolizumab may also be indicated for eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome and chronic rhinosinusitis with nasal polyps. Self-administration may be an option. Check local regulatory and payer criteria, as they may differ from these.

Mechanism: mepolizumab 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.

COPYRIGHTED MATERIAL DO NOT COPY OR DISTRIBUTE
FOR REFERENCE ONLY

Outcomes: Meta-analysis of RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5R led to 47–54% reduction in severe exacerbations. Improvements in quality of life, lung function and symptom control were significant,[39] but less than the clinically important difference. All reduced blood eosinophils; almost completely with benralizumab.[50] In post hoc analyses, clinical outcomes with mepolizumab or benralizumab were similar in patients with and without an allergic phenotype.[51,52] In patients taking OCS, median OCS dose was able to be reduced by ~50% with mepolizumab[53] or benralizumab[54] 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.[55] No differences were seen in lung function, a composite asthma score (CASI), or physician–patient global assessment.[55] In patients with nasal polyps, mepolizumab improved subjective and objective outcomes and reduced the need for surgery,[56,57] and in patients with nasal polyps and severe eosinophilic asthma, benralizumab improved subjective outcomes for both conditions and improved quality of life.[58] See GINA 2023 (Chapter 3.4)[10] for additional details about treatment of nasal polyps.

Potential predictors of good asthma response to anti-IL5 or anti-IL5R:

- Higher blood eosinophils (strongly predictive)[59]
- Higher number of severe exacerbations in previous year (strongly predictive)[59]
- Adult-onset asthma[60]
- Nasal polyposis[52]
- Maintenance OCS at baseline[52]
- Low lung function (FEV_1 <65% predicted in one study).[61]

Adverse effects: In adults, injection site reactions; anaphylaxis rare; adverse events generally similar between active and placebo. In children, more skin/subcutaneous tissue and nervous system disorders (e.g., headache, dizziness, syncope) were seen with mepolizumab than placebo.[55]

Suggested initial trial: at least 4 months

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

Regulatory approvals 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; 300 mg by SC injection every 2 weeks for OCS-dependent severe asthma or if there is concomitant moderate/severe atopic dermatitis. For children 6–11 years with severe eosinophilic/Type 2 asthma by SC injection with dose and frequency depending on weight. May also be indicated for treatment of skin conditions including moderate-to-severe atopic dermatitis, chronic rhinosinusitis with nasal polyps and eosinophilic esophagitis. Self-administration may be an option. Check local regulatory and 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 vary between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, and
- 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 significant,[62] but less than the clinically important difference. In a post hoc analysis, clinical outcomes were similar in patients with allergic and non-allergic phenotype at baseline.[63] In patients with OCS-dependent severe asthma, without minimum requirements for blood eosinophil count or FeNO, the median reduction in OCS dose with anti-IL4Rα versus placebo was 50%.[64] In follow-up, changes were maintained through 2 years of follow-up.[65] In children 6–11 years with eosinophilic/Type 2 asthma, dupilumab reduced severe exacerbation rate and increased lung function; children taking maintenance OCS were excluded.[66] In patients with chronic rhinosinusitis with nasal polyps, dupilumab reduced the size of nasal polyps, improved nasal symptoms and reduced the need for OCS or sinus surgery.[67,68] See GINA 2023 (Chapter 3.4)[10] for additional details about nasal polyps.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVE FOR REFERENCE ONLY

Potential predictors of good asthma response to dupilumab:

- Higher blood eosinophils (strongly predictive)[69]
- Higher FeNO (strongly predictive)[69]

Adverse effects: injection-site reactions; transient blood eosinophilia; rare cases of eosinophilic granulomatosis with polyangiitis (EGPA). 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).

Suggested initial trial: at least 4 months

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

Regulatory approvals 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 regulatory and 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 T2 markers (section 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.[70,71] There was a clear correlation between higher baseline blood eosinophils or FeNO and better clinical outcomes.[71] In patients taking maintenance OCS, anti-TSLP did not lead to a reduced OCS dose compared with placebo.[72]

Potential predictors of good asthma response to anti-TSLP:

- Higher blood eosinophils (strongly predictive)
- Higher FeNO levels (strongly predictive)

Adverse effects: injection site reactions; anaphylaxis is rare; adverse events generally similar between active and placebo groups

Suggested initial trial: at least 4 months

⟶ *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, side-effects, treatment intensity (including OCS dose), and patient satisfaction.
- If the response is unclear, consider extending the trial to 6–12 months.
- 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. 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Care by **SPECIALIST and GP IN COLLABORATION**

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, e.g., Asthma Control Test, Asthma Control Questionnaire (ACQ-5); frequency and severity of exacerbations (e.g., whether OCS were needed), lung function
- Type 2 comorbidities, e.g. nasal polyposis, atopic dermatitis
- Medications: treatment intensity, including dose of OCS, side-effects, affordability
- Patient satisfaction.

⟶ ***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 do not completely stop ICS-containing therapy. Base the order of reduction or cessation of add-on treatments on the observed benefit when they were started, patient risk factors, medication side-effects, cost, and patient satisfaction.

For oral treatments, consider gradually decreasing or stopping OCS first, because of their significant adverse effects. Tapering in severe asthma may be supported by internet-based monitoring of symptom control and FeNO.[73] Monitor patients for risk of adrenal insufficiency, 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.[23]

For inhaled treatments, consider reducing the ICS dose after 3–6 months, but do not completely stop ICS therapy. Current consensus advice is to continue at least medium dose ICS. Patients should be reminded of the importance of continuing their ICS-containing treatment. See GINA 2023 Strategy Report Box 3-16 for more details on stepping down.

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 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,[74,75] 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 randomized controlled trial, significantly more patients who stopped mepolizumab experienced a severe exacerbation within 12 months compared with those who continued treatment. There was a small increase in ACQ-5 but no significant difference between groups.[76] Long-term safety of several biologics has been reported up to 5 or more years.[77-79]

⟶ ***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 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.

COPYRIGHTED MATERIAL NOT TO BE COPIED OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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

- Add-on low-dose azithromycin[32,33] (adults only); first check sputum for atypical mycobacteria and check ECG for long QTc (and re-check EGC after a month); consider potential for antibiotic resistance.
- As last resort, consider add-on low-dose maintenance OCS, but implement strategies such as alternate-day therapy and add-on bisphosphonates to minimize side-effects,[23] and alert patient to the need for additional corticosteroid therapy during illness or surgery.
- Consider bronchial thermoplasty (+ registry). See GINA 2023 Strategy Report page 87.

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 health professionals, to optimize clinical outcomes and patient satisfaction.

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 (GP 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 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

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Glossary of asthma medication classes

For more details, see GINA 2023 Strategy Report (www.ginasthma.org), Product Information from manufacturers, and local eligibility criteria from payers. Always check local eligibility criteria.

Medications	*Action and use*	*Adverse effects*

Medications for maintenance use

Inhaled corticosteroids (ICS)

Examples:
Beclometasone
Budesonide
Ciclesonide
Fluticasone propionate
Fluticasone furoate
Mometasone
Triamcinolone

Inhaler devices: pMDI or DPI

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 2023 GINA Strategy Report p.67 Box 3-14 for low, medium and high doses of different ICS). Adherence with ICS alone (i.e., not in combination with a bronchodilator) is usually very poor.

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.

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

Examples:
Beclometasone-formoterol
Budesonide-formoterol
Fluticasone furoate-vilanterol
Fluticasone propionate-formoterol
Fluticasone propionate-salmeterol
Mometasone-formoterol
Mometasone-indacaterol

Inhaler devices: pMDI or DPI

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: 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. (See section on anti-inflammatory relievers below for as-needed ICS-formoterol in mild asthma; and section on add-on medications for ICS-LABA-LAMA).

The LABA component may be associated with tachycardia, headache or cramps.

LABA is safe for asthma when used in combination with ICS. LABA should not be used without ICS in asthma (or in patients with asthma+COPD) due to increased risk of serious adverse outcomes.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
FOR REFERENCE ONLY

Medications	*Action and use*	*Adverse effects*
Leukotriene modifiers (leukotriene receptor antagonists, LTRA)		
Examples: Montelukast Pranlukast Zafirlukast Zileuton *Tablets*	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	Few in placebo-controlled studies except elevated liver function tests with zileuton and zafirlukast. FDA boxed warning for montelukast about risk of serious behavior and mood changes including in children; should be discussed with patients/parents.

Add-on maintenance treatment

Long-acting muscarinic antagonists (LAMA) – check local eligibility criteria		
Examples: Tiotropium (ages ≥6 years) by mist inhaler, added to ICS-LABA Combination ICS-LABA-LAMA inhalers (adults ≥18 years): Beclometasone-formoterol-glycopyrronium Fluticasone furoate-vilanterol-umeclidinium Mometasone-indacaterol-glycopyrronium *Inhaler devices:* pMDI, DPI or mist inhaler	An add-on option at Step 5 (or, non-preferred, at Step 4) in combination or separate inhalers for patients with uncontrolled asthma despite 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.	Uncommon, but include dry mouth, urinary retention
Anti-IgE – check local eligibility criteria		
Omalizumab (ages ≥6 years) *Subcutaneous injection*	An add-on option for patients with severe allergic asthma uncontrolled on high-dose ICS-LABA. May also be indicated for nasal polyps and chronic spontaneous (idiopathic) urticaria. Self-administration may be an option.	Reactions at the site of injection are common but minor. Anaphylaxis is rare.
Anti-IL5 and anti-IL5R – check local eligibility criteria		
Anti-IL5 Mepolizumab (ages ≥6 years), *subcutaneous injection* Reslizumab (adults ≥18 years), *intravenous infusion* **Anti-IL5 receptor** Benralizumab (ages ≥12 years), *subcutaneous injection*	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 may also be indicated for eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome or chronic rhinosinusitis with nasal polyposis. For mepolizumab and benralizumab, self-administration may be an option.	Headache, and reactions at injection site are common but minor.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Medications	*Action and use*	*Adverse effects*
Anti-interleukin 4 receptor alpha (anti-IL4Rα) – check local eligibility criteria		
Dupilumab (ages ≥6 years) *Subcutaneous injection*	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 skin conditions including moderate-severe atopic dermatitis, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis. Self-administration may be an option.	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 occur.
Anti-TSLP – check local eligibility criteria		
Tezepelumab (ages ≥12 years) *Subcutaneous injection*	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.	Injection-site reactions Anaphylaxis is rare. Adverse events generally similar between active and placebo groups.
Systemic corticosteroids		
Examples: Prednisone Prednisolone Methylprednisolone Hydrocortisone Dexamethasone *Tablets, oral suspension, intramuscular injection, or intravenous injection*	Short-term treatment (in adults, prednisone/prednisolone: usually 5–7 days; dexamethasone: usually 1–2 days) is important in the treatment of severe acute exacerbations, with main effects seen after 4–6 hours. For acute severe exacerbations, OCS therapy is preferred to IM or IV therapy and is effective in preventing short-term relapse. Tapering is required if OCS given for more than 2 weeks. Patients should be reviewed after any exacerbation, to optimize their inhaled therapy in order to reduce the risk of future exacerbations. As a last resort, long-term treatment with OCS may be required for some patients with severe asthma, but 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.	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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
FOR REFERENCE ONLY

Medications	*Action and use*	*Adverse effects*
Anti-inflammatory reliever medications		
Low-dose combination ICS-formoterol reliever		
Beclometasone-formoterol Budesonide-formoterol *Inhaler devices:* pMDI or DPI	This is the reliever inhaler for GINA Track 1, for patients prescribed maintenance and reliever therapy (MART) with 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 patients with mild asthma, as-needed-only ICS-formoterol reduces emergency visits/hospitalizations, compared with daily ICS plus as-needed SABA. Low-dose ICS-formoterol can be taken before exercise to reduce exercise-induced bronchoconstriction, and it can be taken before or during allergen exposure to reduce allergic responses. **Maximum total dose recommended in a single day (maintenance plus reliever doses)** Beclometasone-formoterol: 48 mcg formoterol (delivered dose 36 mcg) Budesonide-formoterol: Adolescents and adults 72 mcg formoterol (delivered dose 54 mcg) Children 6–11 years prescribed MART 48 mcg (delivered dose 36 mcg) **See GINA 2023, Box 3-15 for more details**	As for ICS-formoterol (above)

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Medications	*Action and use*	*Adverse effects*
Low-dose combination ICS-short-acting beta$_2$-agonist (SABA) reliever		
Examples: Budesonide-salbutamol (also described as albuterol-budesonide) Beclometasone-salbutamol *Inhaler device:* pMDI	Anti-inflammatory reliever therapy option for GINA Track 2. Budesonide-salbutamol 100/100 mcg (delivered dose 80/90 mcg) taken 2 inhalations as needed for symptom relief on top of maintenance ICS or ICS-LABA reduced the risk of severe exacerbations in adults compared with SABA reliever; most benefit seen in Step 3. Cannot be used for maintenance and reliever therapy. No evidence for as-needed-only use of budesonide-salbutamol in Steps 1–2. **Recommended maximum doses in any day** Budesonide-salbutamol 100/100 mcg: maximum 6 doses (2 inhalations each dose) in any day (total of 12 inhalations)	As for ICS (above) and short-acting beta$_2$ agonists (below)

Short-acting bronchodilator reliever medications

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

Salbutamol (albuterol) Terbutaline *Inhaler devices:* pMDIs, DPIs (also, rarely, as solution for nebulization) Also (rarely) by injection	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. Currently, inhaled SABAs are the most commonly used bronchodilator for acute exacerbations requiring urgent primary care visit or ED presentation.	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 anticholinergics (also called short-acting muscarinic antagonists)

Examples: Ipratropium bromide Oxitropium bromide May be in combination with SABAs. *Inhaler device:* pMDI or DPI	As-needed use: ipratropium is a less effective reliever medication than SABAs, with slower onset of action. Short-term use in severe acute asthma: adding ipratropium to SABA reduces the risk of hospital admission.	Dryness of the mouth or a bitter taste

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

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). The members of the GINA committees are solely responsible for the statements and recommendations presented in this and other GINA publications. 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 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 Science Committee (2023)
Helen K. Reddel (Australia; Chair), Leonard B. Bacharier (USA), Eric D. Bateman (South Africa), Matteo Bonini (Italy), Louis-Philippe Boulet (Canada), Arnaud Bourdin (France), Chris Brightling (UK), Guy Brusselle (Belgium), Roland Buhl (Germany), Jeffrey M. Drazen (USA), Francine M. Ducharme (Canada), Liesbeth Duijts (The Netherlands), Louise Fleming (UK), Hiromasa Inoue (Japan), Fanny Ko (Hong Kong), Refiloe Masekela (South Africa), Kevin Mortimer (UK), Paulo Pitrez (Brazil), Sundeep Salvi (India), Aziz Sheikh (UK)

GINA Board of Directors (2023)
Arzu Yorgancıoğlu (Turkey; Chair), Keith Allan (UK), Eric D. Bateman (South Africa), Guy Brusselle (Belgium), Muhwa Jeremiah Chakaya (Kenya), Alvaro A. Cruz (Brazil), Hiromasa Inoue (Japan), Jerry A. Krishnan (USA), Mark L Levy (UK), Helen Reddel (Australia)

GINA Dissemination Committee (2023)
Mark L Levy (UK; Chair), Keith Allan (UK), Louis-Philippe Boulet (Canada), Hiromasa Inoue (Japan), Helen Reddel (Australia), Arzu Yorgancıoğlu (Turkey)

GINA Program
Rebecca Decker (GINA Executive Director) Kristi Rurey (GINA Project Manager)
Jenni Harman (Editorial Assistant) Charu Grover (Research Assistant)

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

GINA publications

Global Strategy for Asthma Management and Prevention (2023). 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.

Pocket Guide for asthma management and prevention for adults and children older than 5 years (2023). Summary for primary health care providers, to be used in conjunction with the main GINA report.

Reddel HK, Bateman ED, Schatz M, Krishnan JA, Cloutier MM. A Practical Guide to Implementing SMART in Asthma Management. J Allergy Clin Immunol Pract. 2022 Jan;10(1S):S31-S38. doi: 10.1016/j.jaip.2021.10.011. Epub 2021 Oct 16. PMID: 34666208.

Guidance about COVID-19 and asthma: This slide set provides practical advice about asthma and COVID-19. It is updated as new information is available. www.ginasthma.org/COVID-19/

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. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2023. Updated May 2023. Available from: www.ginasthma.org.

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

12. 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.

13. Hancox RJ, Cowan JO, Flannery EM, et al. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. Respir Med 2000; 94: 767-771.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

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

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

21. 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED FOR REFERENCE ONLY

22. 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. FDA; 2020 [updated 13 March 2020; cited 2023 August]. 3-4-2020 FDA Drug Safety Communication]. 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.

23. 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.

24. Centers for Disease Control and Prevention. Parasites - Stronglyoides. [web page]: U.S. Department of Health & Human Services; 2018 [updated 31 December 2018; cited 2023 August]. Available from: https://www.cdc.gov/parasites/strongyloides/.

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

26. 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.

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

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
UNSCRIPTED - FOR REFERENCE ONLY

43. 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.

44. Hanania NA, Wenzel S, Rosen K, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med 2013; 187: 804-811.

45. Casale TB, Chipps BE, Rosen K, et al. Response to omalizumab using patient enrichment criteria from trials of novel biologics in asthma. Allergy 2018; 73: 490-497.

46. 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.

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

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

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

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

51. 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.

52. 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.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

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

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. 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.

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED FOR REFERENCE ONLY

65. 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.

66. 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.

67. 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-con trolled, parallel-group phase 3 trials. Lancet 2019; 394: 1638-1650.

68. 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.

69. 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.

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

71. 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.

72. 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.

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

74. 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.

75. 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.

76. 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; 69: 2100396.

77. 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.

78. 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.

79. 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.

COPYRIGHTED MATERIAL: DO NOT COPY OR DISTRIBUTE
ARCHIVED FOR REFERENCE ONLY

COPYRIGHTED MATERIAL - DO NOT COPY OR DISTRIBUTE
ARCHIVED - FOR REFERENCE ONLY

Visit the GINA website at www.ginasthma.org

© 2023 Global Initiative for Asthma