GLOBAL INITIATIVE FOR ASTHMA

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A GINA Pocket Guide
For Health Professionals

November 2018

 www.ginasthma.org

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Abbreviations used in this Pocket Guide

+++, ++, +: Plus signs indicate the strength of an association

ABPA: Allergic bronchopulmonary aspergillosis

AERD: Aspirin-exacerbated respiratory disease

ANCA: Antineutrophil cytoplasmic antibody

BNP: B-type natriuretic peptide

CBC: Complete blood count

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CT/HRCT: Computerized tomography; high resolution computerized tomography

CXR: Chest X-ray

DPI: Dry powder inhaler

DLCO: Diffusing capacity in the lung for carbon monoxide

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

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

LABA: Long-acting beta2-agonist

LM/LTRA: Leukotriene modifier/leukotriene receptor antagonist

NSAID: Non-steroidal anti-inflammatory drug

OCS: Oral corticosteroids

OSA: Obstructive sleep apnea

pMDI: Pressurized metered dose inhaler

RCT: Randomized controlled trial

SABA: Short-acting beta2-agonists

SC: Subcutaneous

VCD: Vocal cord dysfunction

Table of Contents

Goal of this Pocket Guide

The goal of this Pocket Guide is to provide a practical summary for health professionals about 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 management of people with asthma.

More details and practical tools for asthma management in clinical practice, particularly for primary care, can be found in the GINA 2018 strategy report and appendix and the online GINA toolbox, available from www.ginasthma.org.

How was the Pocket Guide developed?

The recommendations in this Pocket Guide were based on evidence where good quality systematic reviews or randomized controlled trials or, lacking these, robust observational data, were available, and on consensus by expert clinicians and researchers, where not.

Development of the Pocket 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.

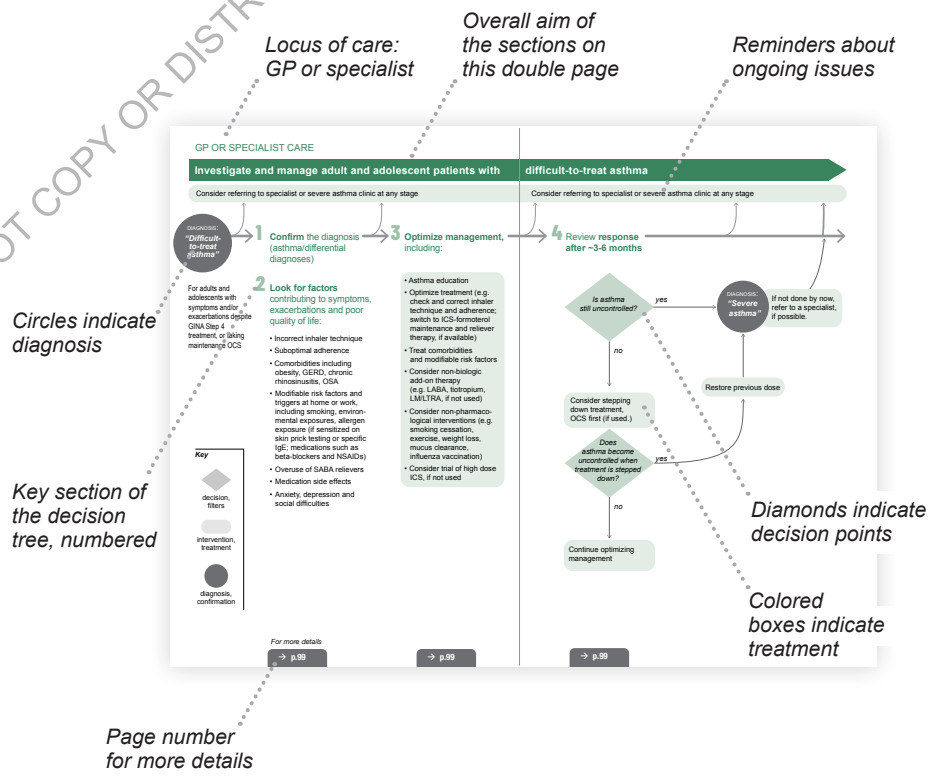
*This **GINA Pocket Guide** is intended as a practical guide for health professionals about the assessment and management of difficult-to-treat and severe asthma. It does NOT contain all of the information required for managing asthma. The Pocket Guide should be used in conjunction with the full GINA 2018 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 Pocket 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 5-7 (blue) are mainly relevant to respiratory specialists
- Section 8 (brown) is about maintaining ongoing collaborative care between the patient, GP, specialist and other health professionals



More detailed information about each of the numbered sections of the decision tree follows on pages 16 to 27.

Key references and additional resources are found at the end of the Pocket Guide, starting on page 28.

Clicking on page/section numbers and citation numbers will take you to the relevant location in the Pocket Guide.

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 oral corticosteroids (OCS), or serious exacerbations (≥1/year) requiring hospitalization

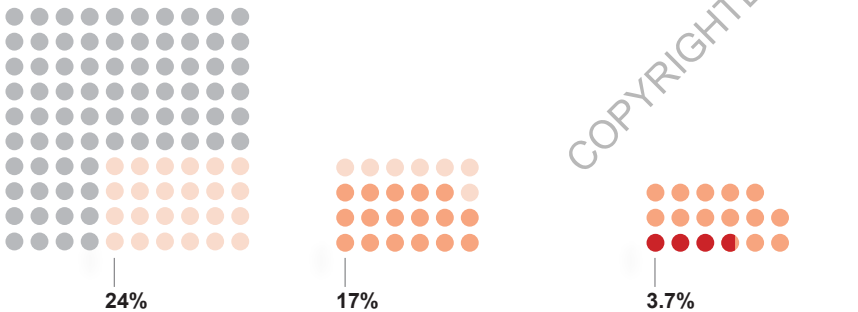
Difficult-to-treat asthma[1] is asthma that is uncontrolled despite GINA Step 4 or 5 treatment (e.g. medium or high dose inhaled corticosteroids (ICS) with a second controller; maintenance OCS), or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. It 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 therapy and treatment 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?

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



These data are from a Dutch population survey of people ≥18 years with asthma[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 OCS include obesity, diabetes, osteoporosis, cataracts diabetes, hypertension and adrenal suppression; psychological side-effects such as depression and anxiety are particularly concerning for patients.[4] Even short-term use of OCS is associated with sleep disturbance, and increased risk of infection, fracture and thromboembolism.[5] 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.[4]

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.

Healthcare utilization and costs

Severe asthma has very high healthcare costs due to medications, physician visits, hospitalizations, and the costs of OCS side-effects. In a UK study, healthcare costs per patient were higher than for type 2 diabetes, stroke, or chronic obstructive pulmonary disease (COPD).[6] In a Canadian study, severe uncontrolled asthma was estimated to account for more than 60% of asthma costs.[7]

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.

Severe asthma decision tree: diagnosis and management

GP OR SPECIALIST CARE

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

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 GINA Step 4 treatment, 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 on skin prick testing or specific IgE); 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)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, 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

Key

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

For more details

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Assess and treat severe asthma phenotypes

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

5 Assess the **severe asthma phenotype** and factors contributing to symptoms, quality of life and exacerbations

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

Type 2 inflammation

Is patient likely to have residual Type 2 airway 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, on lowest possible OCS dose)
Note: these are not the criteria for add-on biologic therapy (see **6b***)*	

- ***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
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- ***Consider need for social/psychological support***
- ***Involve multidisciplinary team care (if available)***
- ***Invite patient to enroll in registry (if available) or clinical trial (if appropriate)***

yes

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis (clinical Type 2 phenotypes with specific add-on treatment)

no

If no evidence of Type 2 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 add-on treatments
  - Trial of tiotropium or macrolide* (if not already tried)
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Stop ineffective add-on therapies
- Consider bronchial thermoplasty (+ registry)

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6a Consider ***non-biologic*** treatments

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

yes

no

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

- Consider higher dose ICS, if not used
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, macrolide*)
- Consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Not currently eligible for biologics

**Off-label*

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Assess and treat severe asthma phenotypes *cont'd*

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

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations and allergic/eosinophilic biomarkers on high dose ICS-LABA, with/without daily OCS [L]
- Consider **local payer eligibility criteria** [L] 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?

Anti-IgE

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

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

What factors may predict good response to anti-IgE?

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

If eligible, trial of **omalizumab** for ≥4 months [L]

Good response?

yes → Good response to T2-targeted therapy

no → **STOP add-on**

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

no → Little/ no response to T2-targeted therapy

no

Anti-IL5 / Anti-IL5R

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

- Exacerbations in last year [L]
- Blood eosinophils ≥300/µl [L]

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

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

If eligible, trial of **anti-IL5** or **anti-IL5R** for ≥4 months [L]

Good response?

yes → Good response to T2-targeted therapy

no → **STOP add-on**

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

no → Little/ no response to T2-targeted therapy

Eligible for neither?

Return to section **6a**

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

For more details

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Monitor / Manage severe asthma treatment

Continue to optimize management

7 Review **response**

- Symptoms
- Exacerbations
- Lung function
- Treatment intensity
- Side-effects
- Affordability
- Patient satisfaction

yes

If good response to Type 2-targeted therapy

- Re-evaluate ongoing therapy every 3-6 months
- For **oral treatments:** consider decreasing/stopping OCS first, then stopping other add-on medication
- For **inhaled treatments:** consider decreasing after 3-6 months; continue at least moderate dose ICS
- Order of reduction based on risks and side-effects, cost and patient preference

If no good response to Type 2-targeted 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 macrolide*
  - Consider add-on low dose OCS, but implement strategies to minimize side-effects
  - Consider bronchoscopy for alternative/additional diagnoses
  - Consider bronchial thermoplasty (+ registry)

no

- Stop ineffective add-on therapies
- Do not stop ICS

For more details

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*Off-label

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

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

Notes:

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Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Care by **GP or SPECIALIST**

1 Confirm the diagnosis (asthma or differential diagnoses)

Difficult-to-treat asthma is defined if the patient has persistent symptoms and/or exacerbations despite prescribing of GINA Step 4-5 treatment (e.g. medium or high dose ICS with another controller such as LABA, or maintenance oral corticosteroids (OCS)). It 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
- 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
- Presence of multiple comorbidities

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. Investigate according to clinical suspicion.

- **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

How can the diagnosis of asthma be confirmed?

Perform spirometry before and after bronchodilator to assess baseline lung function and seek objective evidence of variable expiratory airflow limitation. If initial reversibility testing is negative (<200mL or <12% increase in FEV_1), consider repeating when symptomatic. If spirometry is normal or is not available, provide the patient with a peak flow diary for assessing variability; consider bronchial provocation testing if patient is able to withhold bronchodilators (short-acting beta2-agonist (SABA) for >6 hours, LABA for up to 2 days depending on duration of action).

See GINA 2018 for details about diagnostic testing, and for other objective investigations.

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 and exacerbations

Systematically consider factors that may be contributing to uncontrolled symptoms or exacerbations, or poor quality of life, and that can be treated. The most important modifiable factors include:

- **Incorrect inhaler technique** (seen in up to 80% patients): ask the patient to show you how they use their inhaler; compare with a checklist or video
- **Suboptimal adherence** (up to 75% asthma patients): ask empathically about frequency of use (e.g. 'Many patients don't use their inhaler as prescribed. In the last 4 weeks, how many days a week have you been taking it – not at all, 1 day a week, 2, 3 or more?' or, 'Do you find it easier to remember your inhaler in the morning or the evening?'.[8] 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.
- **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 (often referred to as VCD), 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 non-steroid 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 lack of response,[9] leading in turn to greater use. Overuse may also be habitual. Dispensing of ≥3 SABA canisters per year (average 1.5 puffs per day, or more) is associated with increased risk of ED visit or hospitalization independent of symptoms,[10] and dispensing of ≥12 canisters per year (one a month) increases the risk of death.[11] Risks are higher with nebulized SABA.

continued

- **Anxiety, depression and social and economic problems**: these are very common in patients with difficult asthma[4] 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 itroconazole.

3 Review and optimize management

Review and optimize treatment for asthma, and for comorbidities and risk factors identified in Section 2. For more details, see GINA 2018 Chapter 3.[8]

- **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.[12] Address intentional and unintentional barriers to adherence.[13] For patients with a history of exacerbations, switch to ICS-formoterol maintenance and reliever regimen if available, to reduce the risk of exacerbations.[14]
- **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 (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 non-pharmacologic add-on therapy**, e.g. smoking cessation, physical exercise, healthy diet, weight loss, mucus clearance strategies, influenza vaccination, breathing exercises, allergen avoidance, if feasible, for patients who are sensitized and exposed. For details see GINA 2018 Box 3.9.
- **Consider trial of non-biologic medication** added to medium/high dose ICS, e.g. LABA, tiotropium, leukotriene modifier if not already tried (see Glossary)
- **Consider trial of high dose ICS,** 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

→ *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), then remove other add-on therapy, then decrease ICS dose (do not stop ICS). See GINA 2018 Box 3-7 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.

5 Assess the severe asthma phenotype and other contributors

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, ENT and mental health.

Assessment includes:

- Assessment of the patient's inflammatory phenotype: Type 2 or non-Type 2?
- More detailed assessment of comorbidities and differential diagnoses
- Need for social/psychological support[4]
- Invite patient to enroll in a registry (if available) or clinical trial (if appropriate)

What is Type 2 inflammation?

Type 2 inflammation is found in ~50% 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, although this pathway more typically leads to non-Type 2 inflammation. Type 2 inflammation is often characterized by eosinophils, and may be accompanied by atopy, whereas non-Type 2 inflammation is often characterized by neutrophils.[15] 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 is relatively refractory to high dose ICS. It may respond to OCS but their serious adverse effects[3] mean that alternative treatments should be sought.

Which patients are likely to have refractory 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:

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

These criteria are suggested for initial assessment; the criteria for eligibility for Type 2-targeted biologic therapy may differ - see section **6b** and local criteria. Consider repeating blood eosinophils and FeNO up to 3 times (e.g. when asthma worsens, before giving OCS), before assuming asthma is non-Type 2.

Since OCS rapidly reduce markers of Type 2 inflammation (blood eosinophilia, FeNO) in most patients, these tests should be performed before starting OCS (a short course, or maintenance treatment), or on the lowest possible OCS dose.

Why is the inflammatory phenotype assessed on high dose ICS?

- Most RCT evidence about Type 2 targeted biologics is in such patients
- 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
- Modifiable ICS treatment problems such as poor adherence and incorrect inhaler technique are common causes of uncontrolled Type 2 inflammation

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: CBC, 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
- Other directed testing, e.g. ANCA, CT sinuses, BNP, echocardiogram
- Consider testing for parasitic infections, if Type 2 targeted biologic therapy is considered; this is because parasitic infection may be the cause of the blood eosinophilia, and because Type 2 targeted treatment in a patient with untreated parasitic infection could potentially lead to disseminated disease

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.[4] Consider the need for psychological or psychiatric referral 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.[16]

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 an urgent need for pragmatic clinical trials in severe asthma, including active-controlled studies.

6a If there is NO evidence of Type 2 inflammation

If the patient has no evidence of persistent Type 2 inflammation (section 5):

- **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, 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
- **Consider a trial of non-biologic add-on treatment** if not already tried, e.g. tiotropium, leukotriene modifier, low-dose macrolide[17] (off-label; consider potential for antibiotic resistance). Consider add-on low dose OCS, but implement strategies such as alternate-day treatment to minimize side-effects. Stop ineffective add-on therapies.
- **Consider bronchial thermoplasty**, with registry enrollment. However, the evidence for efficacy and long-term safety is limited.[18,19]

No biologic options are currently available for non-Type 2 severe asthma.

6a Non-biologic options if there IS evidence of Type 2 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 dispensing records, blood prednisone levels,[20] or electronic inhaler monitoring.[21] In one study, suppression of high FeNO after 5 days of directly-observed therapy was an indicator of past poor adherence.[22]
- **Consider clinical Type 2 phenotypes** for which specific add-on treatment is available (see GINA 2018 report Chapter 3D). For example, for aspirin-exacerbated respiratory disease (AERD), consider add-on leukotriene modifier and possibly aspirin desensitization. For allergic bronchopulmonary aspergillosis (ABPA), consider add-on OCS ± anti-fungal agent. For chronic rhinosinusitis and/or nasal polyposis, consider intensive intranasal corticosteroids; surgical advice may be needed. For patients with atopic dermatitis as well as severe asthma, consider add-on dupilumab (anti-IL4-13).
- **Consider increasing the ICS dose** for 3-6 months, and review again

6b 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 eosinophilic and/or allergic biomarkers despite taking high dose ICS-LABA with or without daily OCS.

Where relevant, test for parasitic infection, and treat if present, before commencing Type 2 targeted treatment.

Consider whether to start first with anti-IgE or anti-IL5/5R

When choosing between available therapies, consider the following:

- Does the patient satisfy local payer eligibility criteria?
- Predictors of response (see below)
- Cost
- Dosing frequency
- Delivery route (SC or IV)
- Patient preference

Local payer eligibility criteria for biologic therapy may vary substantially; they are indicated here by the symbol. There is an urgent need for head-to-head comparisons of different biologics in patients eligible for more than one biologic.

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.

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

Currently approved: omalizumab for ages ≥6 years, given by SC injection every 2-4 weeks, with dose based on weight and serum IgE

Mechanism: binds to Fc part of free IgE, preventing binding of IgE to FcεR1 receptors, reducing free IgE and down-regulating receptor expression

Eligibility criteria 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

Write your local eligibility criteria here:

Benefits: RCTs in severe asthma: 34% decrease in severe exacerbations,[23] but no significant difference in symptoms or quality of life.[24] In open-label studies in patients with severe allergic asthma and ≥1 severe exacerbation in last 12 months, there was a 50-65% reduction in exacerbation rate,[25, 26] a significant improvement in quality of life,[25] and 40-50% reduction in OCS dose.[25, 26]

Potential predictors of good response:

- Baseline IgE level does not predict likelihood of response[25]
- In RCTs: a greater decrease in exacerbations was observed (cf. placebo) if blood eosinophils ≥260/µl[27, 28] or FeNO ≥20ppb,[27] but in a large observational study, exacerbations were reduced with both low or high blood eosinophils[26, 29]
- Childhood-onset asthma
- Clinical history suggesting allergen-driven symptoms

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

Suggested initial trial: at least 4 months

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

Currently approved: For ages ≥12 years: L mepolizumab (anti-IL5), 100mg by SC injection 4-weekly, and benralizumab (anti-IL5 receptor α), 30mg by SC injection every 4 weeks for 3 doses then every 8 weeks. For ages ≥18 years: reslizumab (anti-IL5), 3mg/kg by IV infusion every 4 weeks.

Mechanism: mepolizumab and reslizumab bind circulating IL-5; benralizumab binds to IL-5 receptor alpha subunit leading to lysis of eosinophils

Eligibility criteria: these vary by product and between payers, but usually include:

- More than a specified number of severe exacerbations in the last year, L and
- Blood eosinophils above specified level (e.g. ≥300/µl). L In some cases there is a different eosinophil cutpoint for patients taking OCS.

Write your local eligibility criteria here:

Outcomes: RCTs in severe asthma patients with exacerbations in the last year, with varying eosinophil criteria: anti-IL5 and anti-IL5R led to ~55% reduction in severe exacerbations, improved quality of life, and small improvements in lung function and symptom control.[30] All reduced blood eosinophils, almost completely with benralizumab.[30] In patients taking OCS, OCS dose was able to be reduced by 40-60%.

Potential predictors of good response:

- Higher blood eosinophils (strongly predictive)[31]
- Higher number of severe exacerbations in previous year (strongly predictive)[31]
- Adult-onset asthma[32]
- Nasal polyposis, maintenance OCS at baseline[33]

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

Suggested initial trial: at least 4 months

→ *If there is no good response to an initial trial of add-on Type 2 targeted therapy*

- If the response is equivocal, consider extending the trial to 6-12 months L
- If there is no response, stop the biologic therapy
- Consider switching to a trial of a different Type 2 targeted therapy, if available and the patient is eligible; L review response as above

7 Review response and implications for treatment

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

- Symptom control and exacerbations
- Treatment intensity
- Lung function
- 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 (including the biologic) every 3-6 months, but do not completely stop ICS.

Base the order of reduction or cessation of add-on treatments on 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 may be supported by internet-based monitoring of symptom control and FeNO.[34] Monitor patients for risk of adrenal suppression, and provide patient and GP 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.[35]

For inhaled treatments, consider reducing the ICS dose after 3-6 months, but do not completely stop ICS. Current consensus advice is to continue at least medium dose ICS.

For biologic treatments, current consensus advice is that a trial of withdrawal of the biologic may be considered if, after at least 12 months of treatment, 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 limited studies of cessation of biologic therapy.[36, 37]

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

Review the basics for factors contributing to symptoms, exacerbations and poor quality of life (see Section 2): diagnosis, inhaler technique, adherence, modifiable risk factors and triggers including smoking and other environmental exposures at home or work, comorbidities, 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 referral if available, including for diagnosis of alternative conditions.

Reassess treatment options (if not already done), such as add-on low-dose macrolide (off-label; consider potential for antibiotic resistance); consider add-on low-dose maintenance OCS, but implement strategies such as alternate-day therapy and add-on bisphosphonates[35] to minimize side-effects. Consider brochial thermoplasty (+ registry).

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

8 Continue to collaboratively optimize patient care

Ongoing management of a patient with severe asthma involves a **collaboration** between the patient, the GP, 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) - see GINA 2018 report for details
- Comorbidities[16]
- The patient's risk factors for exacerbations
- Treatments (check inhaler technique and adherence; review need for add-on treatments; assess side-effects; optimize comorbidity management and non-pharmacologic strategies)
- The patient's social and emotional needs[4]

The optimal frequency and location of review (GP or specialist) will depend on the patient's asthma control and 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

Glossary of asthma medication classes

For more details, see full GINA 2018 report and Appendix (www.ginasthma.org) and Product Information from manufacturers.

Medications	*Action and use*	*Adverse effects*
Controller Medications		
Inhaled corticosteroids (ICS)		
(pMDIs or DPIs) e.g. beclometasone, budesonide, ciclesonide, fluticasone propionate, fluticasone furoate, mometasone, triamcinolone	ICS are the most effective anti-inflammatory medications for asthma. ICS reduce symptoms, increase lung function, improve quality of life, and reduce the risk of exacerbations and asthma-related hospitalizations or death. ICS differ in their potency and bioavailability, but most of the benefit is seen at low doses (see GINA report Box 3-6 for low, medium and high doses of different ICS).	Most patients using ICS do not experience side-effects. Local side-effects include oropharyngeal candidiasis and dysphonia; these can be reduced by use of 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 and long-acting beta2-agonist bronchodilator combinations (ICS-LABA)		
(pMDIs or DPIs) e.g. beclometasone-formoterol, budesonide-formoterol, fluticasone furoate-vilanterol, fluticasone propionate-formoterol, fluticasone propionate-salmeterol, and mometasone-formoterol.	When a low dose of ICS alone fails to achieve good control of asthma, the addition of LABA to 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 formoterol for maintenance and reliever treatment; and low-dose maintenance ICS-LABA with SABA as reliever.	The LABA component may be associated with tachycardia, headache or cramps. LABA should not be used without ICS in asthma due to increased risk of serious adverse outcomes.
Leukotriene modifiers		
(tablets) e.g. montelukast, pranlukast, zafirlukast, zileuton	Target one part of the inflammatory pathway in asthma. Used as an option for controller therapy, particularly in children. Used alone, they are less effective than low dose ICS; when added to ICS, they are less effective than ICS-LABA.	Few side-effects in placebo-controlled studies except elevated liver function tests with zileuton and zafirlukast.

Medications	*Action and use*	*Adverse effects*
Chromones		
(pMDIs or DPIs) e.g. sodium cromoglycate and nedocromil sodium	Very limited role in long-term treatment of asthma. Weak anti-inflammatory effect, less effective than low-dose ICS. Require meticulous inhaler maintenance.	Side effects are uncommon but include cough on inhalation and pharyngeal discomfort.
Add-on Controller Medications		
Long-acting anticholinergic		
(tiotropium, mist inhaler, ≥6 years)	Add-on option at Step 4 or 5 by mist inhaler for patients with a history of exacerbations despite ICS ± LABA	Side-effects are uncommon but include dry mouth.
Anti-IgE		
(omalizumab, SC, ≥6 years)	An add-on option for patients with severe allergic asthma uncontrolled on high dose ICS-LABA	Reactions at the site of injection are common but minor. Anaphylaxis is rare.
Anti-IL5/anti-IL5R		
(anti-IL5 mepolizumab [SC, ≥12 or ≥6 years], reslizumab [IV, ≥18 years] or anti-IL5 receptor benralizumab [SC, ≥12 years]	Add-on options for patients with severe eosinophilic asthma uncontrolled on high dose ICS-LABA	Headache, and reactions at injection site are common but minor.
Systemic corticosteroids		
(tablets, suspension or IM or IV injection) e.g. prednisone, prednisolone, methylprednisolone, hydrocortisone	Short-term treatment (usually 5–7 days in adults) is important in the treatment of severe acute exacerbations, with main effects seen after 4–6 hours. Oral corticosteroid (OCS) therapy is preferred to IM or IV therapy and is as effective in preventing relapse. Tapering is required if treatment is given for more than 2 weeks. Long-term treatment with OCS may be required for some patients with severe asthma, but side-effects are problematic	Short-term use: some adverse effects e.g. sleep disturbance, GERD, appetite increase, hyperglycaemia, mood changes. Long-term use: limited by significant systemic adverse effects e.g. cataract, glaucoma, hypertension, diabetes, adrenal suppression, osteoporosis. Assess for OCS risk and treat appropriately.

Medications	*Action and use*	*Adverse effects*
Reliever Medications		
Short-acting inhaled beta2-agonist bronchodilators (SABA)		
(pMDIs, DPIs and, rarely, solution for nebulization or injection) e.g. salbutamol (albuterol), terbutaline.	Inhaled SABAs provide quick relief of symptoms and bronchoconstriction including in acute exacerbations, and for pre-treatment of exercise-induced bronchoconstriction. SABAs should be used only as-needed at the lowest dose and frequency required.	Tremor and tachycardia are commonly reported with initial use of SABA. Tolerance to regular use develops rapidly. Excess use, or poor response indicate poor asthma control.
Low-dose ICS-formoterol		
(beclometasone-formoterol or budesonide-formoterol)	This is the reliever medication for patients prescribed maintenance and reliever treatment. It reduces the risk of exacerbations compared with using prn SABA, with similar symptom control.	As for ICS-LABA above
Short-acting anticholinergics		
(pMDIs or DPIs) e.g. ipratropium bromide, oxitropium bromide. May be in combination with SABAs.	Long-term use: ipratropium is a less effective reliever medication than SABAs. Short-term use in acute asthma: inhaled ipratropium added to SABA reduces the risk of hospital admission	Dryness of the mouth or a bitter taste.

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GINA publications

- **Global Strategy for Asthma Management and Prevention** (2018). 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.
- **GINA Online Appendix** (2018). Detailed information to support the main GINA report. Updated yearly.
- **Pocket Guide for asthma management and prevention for adults and children older than 5 years** (2018). Summary for primary health care providers, to be used in conjunction with the main GINA report.
- **Pocket guide for asthma management and prevention in children 5 years and younger** (updated 2017). A summary of patient care information about pre-schoolers with asthma or wheeze, to be used in conjunction with the main GINA report.
- **Diagnosis of asthma-COPD overlap** (2018). This is a stand-alone copy of the corresponding chapter in the main GINA report. It is co-published by GINA and GOLD (Global Initiative for Chronic Obstructive Lung Disease, www.goldcopd.org).
- **Clinical practice aids and implementation tools** are available on the GINA website www.ginasthma.org

Other resources for severe asthma

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

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Notes