

GINA 2021 Executive summary

## **Global Initiative for Asthma (GINA) Strategy 2021 – Executive summary and rationale for key changes**

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**Abstract**

The Global Initiative for Asthma (GINA) Strategy Report provides clinicians with an annually updated evidence-based strategy for asthma management and prevention, which can be adapted for local circumstances (e.g., medication availability). This article summarizes key recommendations from GINA 2021, and the evidence underpinning recent changes.

GINA recommends that asthma in adults and adolescents should not be treated solely with short-acting beta<sub>2</sub>-agonist (SABA), because of the risks of SABA-only treatment and SABA overuse, and evidence for benefit of inhaled corticosteroids (ICS). Large trials show that as-needed combination ICS-formoterol reduces severe exacerbations by  $\geq 60\%$  in mild asthma compared with SABA alone, with similar exacerbation, symptom, lung function and inflammatory outcomes as daily ICS plus as-needed SABA.

Key changes in GINA 2021 include division of the treatment figure for adults and adolescents into two tracks. Track 1 (preferred) has low-dose ICS-formoterol as the reliever at all steps: as-needed only in Steps 1-2 (mild asthma), and with daily maintenance ICS-formoterol (maintenance-and-reliever therapy, MART) in Steps 3-5. Track 2 (alternative) has as-needed SABA across all steps, plus regular ICS (Step 2) or ICS-long-acting beta<sub>2</sub>-agonist (LABA) (Steps 3-5). For adults with moderate-to-severe asthma, GINA makes additional recommendations in Step 5 for add-on long-acting muscarinic antagonists and azithromycin, with add-on biologic therapies for severe asthma. For children 6-11 years, new treatment options are added at Steps 3-4.

Across all age-groups and levels of severity, regular personalized assessment, treatment of modifiable risk factors, self-management education, skills training, appropriate medication adjustment and review remain essential to optimize asthma outcomes.

## Introduction

Asthma is a serious global health problem affecting all age groups.<sup>1</sup> Its prevalence has increased in many countries, especially among children. The Global Initiative for Asthma (GINA) aims to improve the diagnosis, management and prevention of asthma by providing an up-to-date evidence-based strategy and tools and practical resources for clinicians worldwide.

GINA was established through a 1993 collaboration between the World Health Organization (WHO) and the US National Heart, Lung, and Blood Institute to develop a strategy for the diagnosis and management of asthma.<sup>2</sup> The Global Strategy for Asthma Management and Prevention (GINA strategy report) has been updated annually since 2002, to provide clinicians with up-to-date evidence-based recommendations as new evidence emerges and new therapies are approved. The GINA strategy report is under continual review by the Science Committee. GINA methodology<sup>3</sup> involves evaluation of new evidence identified from a twice-yearly rolling review of original research and systematic reviews (not limited to specific PICO [population/intervention/comparison/outcomes] questions), assessment of its impact on existing or new recommendations, and consideration of whether and how it should be integrated into the overall asthma management strategy. GINA is independent of industry.

This article summarizes key recommendations from the 2021 GINA strategy report,<sup>4</sup> published in April 2021, and briefly summarizes the evidence and rationale for recent important changes.

**Key recommendations [text box]**

**1. Diagnosis:** In adults, adolescents and children  $\geq 6$  years, confirm the diagnosis of asthma before starting controller treatment, whenever possible, as it is often more difficult afterwards.

In children  $\leq 5$  years, recurrent wheezing is common, but asthma is more likely if they have wheezing or coughing with exercise/laughing/crying or in the absence of respiratory infections, and if they have a history of eczema or allergic rhinitis.

**2. Personalized assess-treat-review cycles:** Asthma management should be personalized and adjusted in a continual cycle of assessment, treatment and review, to minimize symptoms and prevent exacerbations. Consider symptom control, risk factors for exacerbations and side-effects, lung function, comorbidities, self-management skills, and patient and/or caregiver goals, preferences and satisfaction.

**3. Comprehensive care:** Asthma management is not 'one-size-fits-all'. It includes not only medication, but also treatment of modifiable risk factors and comorbidities, non-pharmacological strategies, and education and skills training, particularly for inhaler technique and adherence.

**4. Inhaled corticosteroids (ICS):** Asthma in adults and adolescents should not be managed solely with short-acting beta<sub>2</sub>-agonists (SABA). Instead, to reduce the risk of severe exacerbations, and to control symptoms, all adults and adolescents with asthma should be treated with ICS-containing therapy: either regularly every day or, in mild asthma, with ICS-formoterol taken as needed for symptom relief. ICS-containing treatment is also recommended for all children 6-11 years with asthma: either regularly or, in mild asthma, by taking ICS whenever SABA is taken. The past distinction between 'intermittent' and 'mild persistent' asthma was arbitrary and does not predict differential response to ICS.

**5. Treatment tracks:** In 2021, for clarity, GINA treatment for adults and adolescents was divided into two tracks, depending on the inhaled reliever medication. Across the five steps, treatment may be stepped up or down within a track, using the same reliever at each step, or switched between tracks, according to the patient's needs and preferences:

- **Track 1, with low-dose ICS-formoterol as the reliever.** This is the overall preferred approach because it reduces the risk of severe exacerbations, compared with using a SABA reliever (with/without maintenance controller), with similar symptom control, similar lung function, and lower oral corticosteroid (OCS) burden. In Steps 1-2, there are additional reasons for preferring as-needed-only ICS-formoterol over as-needed SABA (alone or with daily ICS): (i) Patients with 'mild' asthma can have severe exacerbations, (ii) adherence with daily ICS is almost universally poor in patients with mild or infrequent symptoms, leaving them at higher risk of severe exacerbations, and (iii) starting treatment with SABA alone trains patients to regard it as their main asthma treatment. As-needed-only ICS-formoterol (without maintenance treatment) in Steps 1-2 should be distinguished from Maintenance And Reliever Therapy (MART)\* in Steps 3-5, where patients also take ICS-formoterol as daily maintenance treatment. MART is also an option for children 6-11 years in Steps 3-4. ICS-formoterol should not be used as reliever for patients taking a combination non-formoterol ICS-long-acting beta<sub>2</sub> agonist (LABA), with/without long-acting muscarinic antagonist (LAMA).
- **Track 2, with SABA as the reliever.** This is an alternative approach (e.g., if Track 1 is not possible, or is not preferred by a patient with no exacerbations in the last year). However, before considering a regimen with SABA reliever, consider whether the patient is likely to adhere to controller therapy. If not, they will be exposed to the risks of SABA-only treatment. For Step 1, taking ICS whenever SABA is taken is preferable to SABA alone.

For either track, GINA provides an integrated approach and decision tree for difficult-to-treat and severe asthma, with add-on therapies in Step 5 for severe asthma including biologic therapy guided by inflammatory phenotype.

**6. Children  $\leq 5$  years:** Manage wheezing episodes initially with inhaled SABA. Consider trialing controller therapy (e.g., for 3 months) if the symptom pattern suggests asthma, alternative diagnoses have been excluded, and respiratory symptoms and/or wheezing episodes are frequent or severe.

**7. Stepping up:** Before stepping up treatment to control symptoms or prevent exacerbations, confirm that the symptoms are due to asthma, and identify and address modifiable risk factors including incorrect inhaler technique, poor medication adherence, environmental exposures and multimorbidity, and provide patient education.

**8. Stepping down:** Once asthma is well controlled for 2-3 months, consider stepping down gradually to find the minimum effective dose, monitoring the patient frequently. Step up again if needed.

**9. Asthma action plans:** As part of supported asthma self-management, provide a personalized written asthma action plan for all patients, tailored to their health literacy, so they know how to recognize and respond to worsening asthma.

**10. Referral:** Refer patients for expert advice if any of the following apply:

- The diagnosis of asthma cannot confidently be confirmed. For children  $\leq 5$  years, strongly consider referral for further diagnostic investigations if there is very early onset of symptoms, failure to respond to treatment, or features suggesting alternative diagnoses (e.g., hypoxemia, finger clubbing, failure to thrive).
- Occupational asthma is suspected.

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- The patient has any risk factors for asthma-related death.
- Symptoms or exacerbations remain uncontrolled despite medium/high-dose ICS-LABA.
- The patient needs urgent health care or OCS more than once a year.
- There is evidence or high risk of treatment side-effects.
- Food allergy is suspected.

\*also called single-inhaler maintenance-and-reliever therapy (SMART)

### **Asthma management during the COVID-19 pandemic**

Patients with asthma are not at increased risk of acquiring COVID-19, or of severe COVID-19. Advise patients to continue taking their prescribed asthma medicines, including ICS, alone or in combination with a LABA, and biological therapy for severe asthma.

Avoid the use of nebulizers, where possible, due to the risk of viral transmission. Within healthcare facilities, follow local infection control procedures and COVID-19 testing recommendations if spirometry, peak expiratory flow (PEF) measurement, or other aerosol-generating procedures (e.g., oxygen therapy, sputum induction, ventilation) are needed.

GINA recommends COVID-19 vaccination for people with asthma, with usual precautions including checking for allergy to vaccine ingredients. Anaphylaxis to foods, insect venom or medications is not a contraindication. Consider giving biological therapies on a different day from COVID-19 vaccine.



## Definition, description and diagnosis of asthma

Asthma is a heterogeneous disease defined by the history of respiratory symptoms (e.g., wheeze, shortness of breath, chest tightness and cough) that vary over time and in intensity, together with variable expiratory airflow limitation. Airflow limitation may later become persistent.

Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient for diagnosis. Clinical phenotypes (e.g., childhood-onset versus late-onset, allergic versus nonallergic) do not correlate strongly with specific pathological processes or treatment responses.

The diagnosis of asthma is based on a history of characteristic symptom patterns and evidence of variable expiratory airflow limitation from bronchodilator reversibility testing or from other tests such as positive bronchial provocation test, excessive variability on PEF monitoring, excessive variation in forced expiratory volume in 1 second (FEV<sub>1</sub>) between visits, or a significant increase in FEV<sub>1</sub> after ICS treatment ([Table E1](#) in online data supplement). Explain to patients that often, more than one of these tests is needed<sup>5</sup>. Evidence for the diagnosis of asthma should be confirmed before starting controller treatment, if possible, to avoid inappropriate treatment or missing other important diagnoses, and because diagnosis is often more difficult later. Clinical examination, including chest auscultation, may be completely normal.

Fractional concentration of exhaled nitric oxide (FeNO) is higher in asthma with Type 2 airway inflammation, but also in atopy, allergic rhinitis, eczema and eosinophilic bronchitis, and it is lower during bronchoconstriction and in some asthma phenotypes (e.g., neutrophilic asthma). It can be increased or decreased by viral respiratory infections.

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Additional strategies may be needed to confirm the diagnosis of asthma in particular populations, including patients already on controller treatment (GINA 2021, Box 1-3), the elderly, smokers, and those in low-resource settings. The differential diagnosis of asthma varies by age (GINA 2021, Box 1-5).

### Assessment of asthma

Asthma control is defined as the extent to which the features of asthma are apparent or have been reduced or eliminated by controller treatment<sup>6</sup>. Assess asthma control within two domains: symptom control, and risk of adverse outcomes, particularly exacerbations.

#### Symptom control

Assess symptom control from asthma-related symptom frequency, night-waking and activity limitation, and, for patients using SABA reliever, frequency of SABA use ([Figure 1](#)). Other symptom control tools include Asthma Control Test<sup>7</sup> and Asthma Control Questionnaire (preferably the 5-item version, i.e. ACQ-5).<sup>8</sup>

*Rationale:* Historically, frequency of SABA reliever use (<2 or ≥2 days/week) was included in the composite assessment of symptom control. This distinction was arbitrary, based on the assumption that if SABA was used on >2 days in a week, the patient needed to start controller therapy or increase the dose. However, if a patient uses as-needed ICS-formoterol as their reliever on average >2 days/week, this is already providing additional controller therapy, so further dose escalation may not be needed. Therefore, use of ICS-formoterol reliever ≤2 versus >2 days/week is not included in the composite assessment of symptom control. Instead, average frequency of ICS-formoterol use over the past 4 weeks should be assessed separately when the patient's maintenance controller dose is reviewed.

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**Risk factors**

Assess every patient's risk of exacerbations, even when symptom control is good. Although patients with poor symptom control are more likely to have exacerbations, patients with few or no symptoms can still have severe or even fatal exacerbations, including with external triggers such as viral respiratory infections.<sup>9</sup> Factors that increase a patient's risk of exacerbations even if they have few symptoms include  $\geq 1$  exacerbation in the previous year, over-use of SABA (e.g.,  $\geq 3$  x 200-dose albuterol [salbutamol] canisters/year, i.e., average more than daily use), inadequate ICS use (under-treatment, poor adherence, incorrect inhaler technique), some comorbidities (including obesity, chronic rhinosinusitis, gastroesophageal reflux, confirmed food allergy), low FEV<sub>1</sub>, high blood eosinophil count in patients with Type 2 inflammation, and major psychological or socioeconomic problems. Also assess risk factors for persistent airflow limitation and medication side-effects ([Figure 1](#)).

**Lung function testing**

Record lung function at diagnosis, 3-6 months after starting treatment, and then periodically (e.g., at least once every 1-2 years; more often in at-risk patients and those with severe asthma), to identify progressive decline. Lung function at individual visits is of limited use for guiding treatment because of its large (up to 20%) visit-to-visit variation.<sup>10</sup> Investigate further if there are few symptoms but impaired lung function, which may indicate poor perception<sup>11</sup> or long-term adaptation; or frequent symptoms despite good lung function, which may indicate an alternative cause for the symptoms (GINA 2021, Box 1-5).

**Asthma severity**

By consensus<sup>6</sup>, asthma severity is assessed retrospectively, after at least 2-3 months of treatment, from the level of treatment required to control symptoms and exacerbations. GINA does not distinguish between so-called 'intermittent' and 'mild persistent' asthma because this

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historical distinction was arbitrary, with no evidence of a difference in treatment response. Severe asthma is asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires such treatment to prevent it becoming uncontrolled.<sup>12</sup> It is important to distinguish between severe asthma and difficult-to-treat asthma, i.e., asthma that is uncontrolled due to other factors, such as incorrect inhaler technique, poor adherence, and comorbidities such as obesity, and environmental exposures.<sup>13</sup>

*Rationale:* This definition of asthma severity works well at the severe end of the spectrum but is less useful for describing mild asthma (see *Topics requiring further research*). For example, patients with infrequent or no interval symptoms can still have severe exacerbations. This risk is reduced to a similar extent by either daily ICS treatment<sup>14, 15</sup> or by ICS-formoterol taken only for symptom relief,<sup>15</sup> and baseline symptom frequency does not predict need for daily ICS.<sup>15, 16</sup>

## **General principles of asthma management**

The goals of asthma management are to achieve good symptom control, relieve symptoms when they occur, and minimize risk of exacerbations and asthma-related death, persistent airflow limitation and side-effects of treatment. The patient's own treatment goals should be identified because they may be different. Effective asthma management requires a partnership between the patient (or parent/caregiver) and healthcare providers, with shared decision-making and good communication.

Asthma management is not 'one-size-fits-all', but instead should be personalized and adjusted in a continual cycle of assessment, treatment adjustment, and review ([Figure 2](#)).

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**Assessment**

Assess not only symptom control and lung function, but also the individual's modifiable risk factors and comorbidities (also called 'treatable traits'),<sup>17</sup> and patient/parent goals and preferences. Check adherence and inhaler technique frequently. Poor symptom control is associated with much higher risk of exacerbations, but patients with apparently mild asthma or with good symptom control can still have severe or life-threatening exacerbations.<sup>9, 14, 18</sup>

**Treatment adjustment**

Treatment adjustment includes not only changes in asthma medication dose or type, but also multidisciplinary management of modifiable risk factors and comorbidities (GINA 2021, Section 3D), and non-pharmacological strategies such as smoking cessation and avoidance of indoor/outdoor air pollution (GINA 2021, Box 3-9).

For all patients, provide regular training in inhaler technique and asthma self-management, including self-monitoring of symptoms and/or PEF, and a written asthma action plan<sup>19</sup> (GINA 2021, Section 3C). Encourage adherence with controller medication, even when symptoms are infrequent. Consider stepping down treatment when good control has been maintained for 2-3 months (GINA 2021, Box 3-7).

**Review**

Arrange regular medical review to identify modifiable risk factors, optimize care and minimize the risk of exacerbations: review at least yearly (more often in patients with moderate or severe asthma), after an exacerbation, and after a treatment change. Review clinical outcomes and side effects, patient/parent/caregiver satisfaction, inhaler technique and self-management skills. Ensure the patient/caregiver has an up-to-date written asthma action plan.

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*Rationale:* The GINA strategy ([Figure 2](#)) considers not only patient characteristics that may predict a clinically important difference in treatment response, but also medication access, the patient's preferences, and practical issues of cost, ability to use the inhaler, and likely adherence. The extent to which asthma treatment can be individualized according to patient characteristics or phenotype depends on the health system, the clinical context, evidence about the magnitude of potential difference in outcomes, cost, and available resources.

## Medications and strategies for symptom control and risk reduction

Asthma medications are categorized as controllers, relievers, and add-on therapies:

- **Controllers** contain ICS, which reduce airway inflammation, control symptoms, and reduce the risks of exacerbations<sup>20</sup>, even in mild asthma,<sup>14, 15, 21</sup> and of asthma death.<sup>22</sup> Treatment with ICS may reduce exacerbation-related decline in lung function.<sup>23</sup> 'Maintenance' therapies are controllers that are prescribed for daily use.
- **Relievers** (low-dose ICS-formoterol or SABA) contain rapid-onset bronchodilators. They are used 'as needed', i.e., for quick relief of symptoms, including during exacerbations. Using ICS-formoterol as reliever (often called an 'anti-inflammatory reliever' or AIR) also reduces the risk of severe exacerbations, compared with SABA reliever, both with<sup>24, 25</sup> or without<sup>15, 21</sup> maintenance controller treatment. SABA or ICS-formoterol is also recommended before exercise if needed to prevent exercise-induced bronchoconstriction.<sup>26, 27</sup>
- **Add-on therapies** are mainly for patients with difficult-to-treat or severe asthma (see below).

When choosing medications, consider local guidelines, regulatory approvals and payer

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criteria.

### **Recommendation against SABA-only treatment**

Since 2019, GINA has recommended against SABA-only treatment of asthma in adults and adolescents, after consideration of its risks and the evidence for a safer alternative.<sup>28</sup> Instead, to reduce the risk of serious exacerbations and control symptoms, all adults and adolescents with asthma should receive ICS-containing treatment, either regularly or, in mild asthma, symptom-driven<sup>28</sup>. ICS is now also recommended for all children 6-11 years with asthma, either regularly or, in mild asthma, whenever SABA is taken for symptom relief.

*Rationale:* Although SABA is inexpensive and relieves symptoms quickly, treatment of asthma with SABA alone is associated with increased risk of asthma-related death<sup>22</sup> and of urgent asthma-related healthcare,<sup>20</sup> even in patients with so-called 'intermittent' asthma.<sup>29</sup> Overuse of SABAs ( $\geq 3$  x 200-dose albuterol canisters/year) is associated with incrementally increasing risk of asthma exacerbations and mortality, including in patients treated with SABA alone.<sup>22</sup> Regular use of SABA, even 2-4 times/day for 1-2 weeks, is associated with beta<sub>2</sub> receptor downregulation, loss of bronchodilator response, increased airway hyperresponsiveness, and increased airway inflammation.<sup>30, 31</sup> Importantly, from a cognitive and behavioral perspective, starting treatment with SABA alone trains the patient to regard it as their main asthma treatment, increasing the challenges for adherence with any subsequent advice to take ICS every day even when asymptomatic.

By contrast, in mild asthma, as-needed ICS-formoterol decreases the risk of severe exacerbations requiring OCS by  $\geq 60\%$  compared with SABA alone,<sup>15, 21</sup> including in patients without elevated Type 2 inflammatory markers,<sup>15, 32</sup> with a very small average daily ICS dose.<sup>15, 16, 21, 33</sup> Starting treatment with as-needed ICS-formoterol in patients with mild asthma addresses both symptom relief and risk reduction, without the need for daily maintenance

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treatment.

### **GINA treatment tracks for adults and adolescents**

There are five levels of treatment (Steps 1-5; [Figure 3](#)), with two ‘tracks’, depending on the choice of reliever: ICS-formoterol (Track 1, preferred) or SABA (Track 2, alternative).

Treatment may be stepped up or down within a track using the same reliever at each step, or switched between tracks.

Within **Track 1**, the reliever is as-needed low-dose ICS-formoterol. This means that when a patient at any treatment step has asthma symptoms, they take low-dose ICS-formoterol for symptom relief. In Steps 1-2, this also provides the patient’s controller therapy and reduces severe exacerbation risk,<sup>15, 16, 21, 33</sup> without daily maintenance treatment. This is distinguished from Maintenance-And-Reliever Therapy (MART) in Steps 3-5, where patients take ICS-formoterol both as daily maintenance treatment and, as needed, for symptom relief ([Table 1](#)).

**Track 2**, with SABA reliever, is suggested where ICS-formoterol is not available, or is not preferred by a patient at low risk of exacerbations (including having no exacerbations in the past year). Before prescribing therapy with SABA reliever, consider if the patient is likely to be poorly adherent with ICS controller therapy, as this increases the risk of exacerbations.

In [Figure 3](#), additional or alternative treatments with less evidence for safety, efficacy and/or effectiveness are shown as ‘other controller options’.

*Rationale:* GINA introduced two tracks into the 2021 treatment figure for adults and adolescents ([Figure 3](#)) to clarify:

- how to step treatment up or down within the different reliever options (ICS-formoterol or SABA)



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- that SABA is the recommended reliever for patients prescribed maintenance non-formoterol ICS-LABA.

The Track 1 approach is preferred overall because it reduces the risk of severe exacerbations compared with using a SABA reliever, with similar symptom control and lung function, and it integrates messaging about the importance of both symptom control and risk reduction across all treatment steps, including Step 1. The figure also summarizes the main considerations for choosing ICS-formoterol or SABA as reliever, and reinforces the key elements of personalized asthma treatment.

**GINA treatment steps for adults and adolescents (Figure 3)**

**Steps 1 and 2 preferred treatment (Track 1):** The preferred treatment for adults and adolescents with mild asthma is low-dose ICS-formoterol taken as needed for symptom relief, without maintenance treatment. As-needed-only ICS-formoterol is usually prescribed as budesonide-formoterol 200/6 mcg metered dose (160/4.5 mcg delivered dose) 1 inhalation as needed (Table 1; for dosage details see Table E2 and [downloadable resource](#)). Other combination ICS-formoterol products may be suitable but have not yet been studied.

*Rationale:* Considerations for the recommendations at Steps 1 and 2 are interrelated. In patients eligible for **Step 2** treatment, two large studies found that as-needed ICS-formoterol reduced the risk of severe exacerbations by almost two-thirds compared with SABA-only treatment.<sup>15, 21</sup> Four studies (~10,000 patients) showed a similar or greater reduction in severe exacerbations compared with daily low-dose ICS, without clinically important differences in symptom control,<sup>15, 16, 21, 33</sup> lung function,<sup>15, 16, 21, 33</sup> or airway inflammation measured by FeNO<sup>15, 16</sup> over 12 months. The primary outcome variable of one study<sup>21</sup> was ‘well-controlled asthma weeks’, but this outcome was not considered reliable because it was based on a past definition of asthma control, and was systematically biased against the as-needed ICS-

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formoterol treatment group in which patients were permitted much less ICS than those on maintenance ICS before a week was classified as not well-controlled. In two studies that showed greater overall reduction in risk of severe exacerbations reduction with as-needed ICS-formoterol compared with maintenance ICS plus as-needed SABA,<sup>15, 16</sup> no predictors of differential response were identified among many baseline characteristics, including inflammatory phenotype,<sup>15, 16</sup> except for a clinically unimportant difference in ACQ-5 in one study.<sup>16</sup>

In **Step 1**, the recommendation for as-needed low-dose ICS-formoterol for adults and adolescents with symptoms less than twice/month is supported by indirect evidence for a large reduction in risk of severe exacerbations, compared with as-needed SABA alone.<sup>15, 21</sup> Extension of this recommendation to Step 1 was also supported by several important considerations:

- Historically, recommendations for as-needed SABA alone were never supported by evidence of long-term safety or efficacy; early guidelines had assumed that patients with mild asthma would not benefit from ICS, and were concerned about its risks based on experience with OCS.
- The past distinction between eligibility for Step 1 and Step 2 treatment based on symptom frequency (e.g.,  $\leq$  or  $>2$  days/week) was arbitrary, not evidence-based.
- The use of as-needed ICS-formoterol markedly reduces severe exacerbations, compared with as-needed SABA, even in patients with SABA use  $\leq 2$ /week at baseline (so-called ‘intermittent’ asthma)<sup>15</sup>.
- A single day with  $>2$ ,  $>4$ ,  $>6$  or  $>8$  doses of as-needed budesonide-formoterol reduced the short-term (21-day) risk of severe exacerbations, compared with as-needed SABA alone (*post hoc* analysis).<sup>34</sup> A similar effect was seen with ICS-formoterol MART in

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Steps 3-4.<sup>35, 36</sup>

- Even modest over-use of SABA (e.g., dispensing  $\geq 3$  albuterol canisters/year, i.e., average  $\geq 1.6$  puffs/day) is associated with increased risk of severe exacerbations<sup>37</sup> and, in one study, higher asthma mortality.<sup>38</sup>
- Even occasional short courses of OCS (e.g., 4-5 courses over 7 years, i.e.,  $< 1$  course/year), are associated with significant short-term risks<sup>39</sup> and cumulative risks of long-term adverse effects such as osteoporosis and diabetes.<sup>40</sup>
- Regular daily low-dose ICS treatment is highly effective in reducing asthma symptoms and risk, including in patients with infrequent symptoms, but poor adherence to ICS is common<sup>41</sup>, exposing patients to the risks of SABA-only treatment.
- As-needed budesonide-formoterol is well tolerated in mild asthma.<sup>15, 16, 21, 33</sup>
- Starting treatment with SABA alone trains the patient to regard it as their primary asthma treatment.

**Steps 1 & 2 alternative treatment (track 2):** The Step 2 recommendation for adults and adolescents remains regular low-dose ICS with as-needed SABA. The Step 1 recommendation is taking ICS whenever SABA is taken (combination or separate inhalers).

*Rationale:* For patients with initial symptoms twice/month or more, low-dose maintenance ICS reduces the risk of serious exacerbations by almost half compared with SABA alone.<sup>14</sup> There is a paucity of evidence for safety and effectiveness of as-needed concomitant ICS+SABA, as only small groups received this regimen in studies of adults<sup>42, 43</sup> and children 5-18 years.<sup>44, 45</sup> However, it would be preferable to SABA alone if ICS-formoterol is not available or affordable. No data are available about the acceptability to adults of carrying separate ICS and SABA inhalers for symptom relief, or what proportion of patients revert to SABA-only use. No data are available about safe levels of as-needed ICS+SABA use, but in

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one study, exacerbations were higher among patients randomized to twice-daily ICS-SABA than those on as-needed ICS-SABA,<sup>42</sup> consistent with risks associated with SABA overuse.<sup>38</sup>

**Steps 3 and 4:** The preferred Step 3 treatment is maintenance and reliever therapy with low-dose ICS-formoterol (MART),<sup>24, 25, 46</sup> which is approved in many countries with budesonide-formoterol and beclometasone-formoterol. For Step 4, if needed, the maintenance dose of ICS-formoterol can be increased to medium.<sup>36, 47, 48</sup> The doses of ICS-formoterol recommended for MART, including the maximum dose in any day, are shown in [Table E2](#) and the [downloadable resource](#).

*Rationale:* In adults and adolescents with poor symptom control and  $\geq 1$  exacerbation in the previous year, MART reduced exacerbations and provided similar symptom control at relatively low ICS doses, compared with maintenance ICS-LABA or higher-dose ICS, both with as-needed SABA.<sup>24, 49-51</sup> In open-label studies in broader populations, MART also significantly reduced severe exacerbations, with a lower average dose of ICS.<sup>25, 46</sup> ICS-formoterol should not be used as the reliever for patients taking maintenance non-formoterol ICS-LABA, because there are no data for efficacy and safety.

**Step 5:** [See Difficult-to-treat and severe asthma](#), below.

**Choosing initial asthma treatment:** when choosing the track and starting step for initial treatment (GINA 2021, Boxes 3-4A-D), consider not only the patient's current symptoms and risk of exacerbations, but also practical issues including medication access (availability and cost), inhaler technique, likely adherence, and patient preferences. Before starting, record evidence for the diagnosis of asthma, the patient's symptom control and risk factors, including lung function, and check that they can use the inhaler correctly. Provide education and skills training, and schedule a follow-up visit to assess response ([Figure 2](#)).

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During ongoing treatment, medication may be adjusted up or down within the same track (i.e., with the same reliever) or may be switched between tracks, depending on patient needs. However, for patients prescribed as-needed-only ICS-formoterol (Steps 1-2) or MART (Steps 3-5), beware of risks to the patient if their ICS-formoterol is switched without consultation (e.g., in health systems where medication substitution by pharmacists or nurses is permitted) to a combination non-formoterol ICS-LABA, as these are not suitable for as-needed use.

**Stepping down to find the minimum effective dose:** When good asthma control has been achieved and maintained for 2-3 months, consider stepping down to find the lowest effective step. Do not completely withdraw ICS, except if needed temporarily while confirming the diagnosis of asthma. Adults and adolescents with well-controlled asthma while on daily low-dose controller therapy can step down to either as-needed ICS-formoterol<sup>16, 21, 33</sup> or to as-needed ICS+SABA taken together<sup>42, 43</sup> (GINA 2021, Box 3-7).

**Stepping up if asthma remains uncontrolled:** Before considering any sustained step up, first check inhaler technique, adherence, persistent allergen exposure and comorbidities.

There is no evidence to support specific recommendations about when to increase from as-needed-only ICS-formoterol in Steps 1-2 to Step 3 MART by adding maintenance ICS-formoterol, but it should be prompted by factors such as ongoing use of as-needed ICS-formoterol on most days/week or further exacerbations.

**Patients with risk factors for exacerbations:** Prescribe an ICS-containing controller, preferably with ICS-formoterol as reliever, as this reduces the risk of severe exacerbations<sup>15, 16, 21, 24, 25, 33, 46</sup>. Arrange review more frequently than for patients at low risk. Identify and address modifiable risk factors, e.g., smoking, over-use of SABA, comorbidities (GINA 2021, Box 3-8). Consider non-pharmacological strategies, such as smoking cessation advice and

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trigger avoidance, to improve symptom control and/or reduce risk (GINA 2021, Box 3-9).

**Management of exercise-induced symptoms:** For patients with dyspnea or wheezing on exertion, distinguish between exercise-induced bronchoconstriction and symptoms due to obesity, poor cardiopulmonary fitness, or alternative diagnoses such as inducible laryngeal obstruction. For patients with exercise-induced bronchoconstriction, prescribe ICS-containing controller treatment and advise sufficient warm-up before exercise.<sup>26</sup> Patients using as-needed ICS-formoterol as their reliever (Track 1) can use the same medication before exercise, if needed, and do not need a SABA inhaler.<sup>27</sup>

*Rationale:* For pre-exercise use by adults and adolescents, formoterol was recommended in guidelines for many years as an effective and safe alternative to albuterol,<sup>26</sup> but is no longer promoted because of risks of LABA-only treatment. Pre-exercise ICS-formoterol avoids this risk and is as effective as daily ICS plus pre-exercise SABA in reducing exercise-induced bronchoconstriction.<sup>27</sup>

### **GINA steps for children aged 6-11**

Treatment steps for children are shown in [Figure 4](#). In Step 1, for children with initial symptoms <twice/month, taking ICS whenever SABA is taken for symptom relief is preferred over regular ICS or as-needed SABA alone. Regular low-dose ICS with as-needed SABA is recommended in Step 2 for most children with asthma, but attention must be paid to adherence.

In Step 3, options include low-dose ICS-LABA, medium-dose ICS or very low-dose budesonide-formoterol MART.<sup>52</sup> In Step 4, options include medium-dose ICS-LABA<sup>53</sup> or low-dose MART ([Table 1](#), [Table E2](#) and [downloadable resource](#)). For all children at Step 4, consider referral for expert advice. In children, before stepping up, consider trying other controller options at the same step.

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*Rationale:* The addition of as-needed concomitant ICS+SABA as anti-inflammatory reliever in Step 1 for children was based on evidence from two studies in which children and adolescents were stepped down from regular ICS to as-needed ICS plus SABA in separate inhalers,<sup>44, 45</sup> and because of likely nonadherence with daily ICS by children with infrequent symptoms. For Step 2, there is much more evidence for safety and effectiveness of low-dose ICS, but in the real world, ICS adherence is extremely low. In Step 3, maintenance and reliever therapy (MART) with very low-dose ICS-formoterol<sup>52</sup> was previously recommended in the GINA report text, and for consistency is now also included in the figure. For Step 4, doubling the MART maintenance dose to 100/6 mcg (delivered dose 80/4.5 mcg) 1 inhalation twice daily (still ‘low dose’) was included by consensus, given the variation in ICS responsiveness between patients ([Table 1](#), [Table E2](#) and [downloadable resource](#)).

### **Managing asthma with comorbidities and in specific populations**

Identify and manage comorbidities such as rhinosinusitis, obesity and gastro-esophageal reflux disease. Multimorbidity contributes to respiratory symptoms and impaired quality of life, and some comorbidities contribute to poor symptom control or exacerbations.

Despite general concerns about medication use in pregnancy, the advantages of actively treating asthma in pregnancy to avoid exacerbations markedly outweigh any potential adverse effects of usual controller and reliever medications.<sup>54</sup>

For details of multi-disciplinary assessment and management of asthma with comorbidities and in specific settings, see GINA 2021, Chapter 3D.

## **Diagnosis and initial treatment of patients with features of both asthma and COPD**

Asthma and chronic obstructive pulmonary disease (COPD) are umbrella labels for overlapping heterogeneous conditions. Symptoms may be similar, and the diagnostic criteria overlap. Some patients have features of both asthma and COPD ('asthma+COPD'), particularly smokers and older adults. This is not a single disease entity. It includes several clinical phenotypes that are likely caused by a range of underlying mechanisms.

There are important differences in evidence-based treatment recommendations for asthma<sup>4</sup> versus COPD,<sup>55</sup> with treatment with long-acting bronchodilators alone (i.e., without ICS) recommended as initial treatment in COPD, but contraindicated in asthma due to the risk of severe exacerbations and death. Until more discriminatory risk factors are identified, all patients with diagnoses of both asthma and COPD should receive ICS. COPD should be managed according to Global Initiative for Chronic Obstructive Lung Disease (GOLD)<sup>55</sup> recommendations. For all patients, provide education on inhaler technique and adherence, and advice about smoking cessation, immunizations, physical activity, and management of comorbidities. Refer for specialist investigations and multi-disciplinary care, where possible.

*Rationale:* The descriptive term 'asthma+COPD' is preferred because 'asthma-COPD overlap' (ACO) was often assumed to represent a single disease. Patients with asthma+COPD have a greater burden of symptoms, exacerbations, impaired quality of life, more rapid decline in lung function, need for healthcare utilization and higher mortality compared with patients with asthma or COPD alone.<sup>4</sup> The recommendation for ICS is because several studies have shown that patients with diagnoses of both asthma and COPD are at increased risk of hospitalization or death if they are treated with LABA compared with ICS-LABA.<sup>56-58</sup>



## Difficult-to-treat and severe asthma in adults and adolescents

Detailed information is provided in the GINA 2021 pocket guide on difficult-to-treat and severe asthma (<https://ginasthma.org/reports>), including an integrated decision tree for diagnosis and management across primary and specialist care. A brief summary is included below.

### Assessment and optimization of therapy

**Difficult-to-treat asthma** is asthma that is uncontrolled despite medium- or high-dose ICS-LABA treatment, or that requires high-dose ICS-LABA treatment to maintain good symptom control and reduce exacerbations.

**Severe asthma** is asthma that is uncontrolled despite good adherence with optimized high-dose ICS-LABA therapy and management of contributory factors, or that worsens when high-dose treatment is decreased. Approximately 3-10% of people with asthma have severe asthma.<sup>12, 59</sup>

Assess all patients with difficult-to-treat asthma to confirm the diagnosis of asthma, and to identify and manage factors that commonly contribute to symptoms, poor quality of life, and/or exacerbations. For patients with persistent symptoms and/or exacerbations despite high-dose ICS-LABA, assess the clinical and inflammatory phenotype, as this may guide the selection of add-on treatment. Refer for expert advice if asthma does not improve in response to optimizing Step 4 or 5 treatment (or earlier, if needed).

### Management of severe asthma

Refer patients to support services, where available, to help them deal with the heavy physical,

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emotional, social and financial burden of severe asthma and its treatment.<sup>60</sup>

In Step 5, recommended add-on options include LAMA (tiotropium  $\geq 6$  years, triple therapy with ICS-LABA-LAMA  $\geq 18$  years). Adding LAMA provided modest improvement in lung function but not symptom control, and exacerbations were reduced in some studies.<sup>61-65</sup> Step 4 MART with ICS-formoterol should be tried before considering add-on LAMA; as-needed ICS-formoterol can be continued as the reliever for patients prescribed ICS-formoterol-LAMA, but for patients prescribed an ICS-LABA-LAMA with non-formoterol LABA, the appropriate reliever is SABA. After specialist referral, add-on low-dose azithromycin is another option for reducing exacerbations, but risks of antibiotic resistance and prolonged QTc interval must be considered.<sup>66</sup> Sputum-guided adjustment of ICS dose improves outcomes in moderate-to-severe asthma,<sup>67</sup> but is not widely available and the optimal frequency of sputum assessment is not known.

With add-on biologic therapies for severe eosinophilic asthma (benralizumab, dupilumab, mepolizumab, reslizumab) and severe allergic asthma (dupilumab, omalizumab) the main benefits are substantial reduction in severe exacerbation and reduced OCS exposure.<sup>68</sup> No head-to-head studies are available, but typical eligibility criteria for each class, and predictors of good response, are found in the GINA pocket guide decision tree.<sup>13</sup>

Maintenance OCS treatment should be avoided, wherever possible, because of its serious long-term side-effects.<sup>40, 69</sup>

At follow-up, assess the response to any add-on treatment, stop ineffective treatments, and consider other options. For patients who respond to add-on therapy, re-evaluate need for other therapies every 3-4 months, but do not completely stop ICS.

Continue to optimize patient care in collaboration with primary care, and consider the

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patient's social and emotional needs. Arrange multidisciplinary team care for severe asthma, if available. Invite patients with severe asthma to enroll in a registry or clinical trial, if available and relevant, to help fill evidence gaps, including comparison of biologic therapy options and positioning of bronchial thermoplasty.<sup>68</sup>

## Management of worsening asthma and exacerbations

Asthma exacerbations represent acute or sub-acute worsening in symptoms and lung function from the patient's usual status. In some cases, a patient may present for the first time during an exacerbation.

For discussion with patients, use terminology that is easily understood; 'flare-up' is more patient-friendly than the academic term 'exacerbation'. The terms 'episodes', 'attacks' and 'acute asthma' are often used, but their meanings vary widely.<sup>70</sup>

Preventing severe exacerbations that require treatment with systemic corticosteroids is an important goal of asthma management. Even a single OCS course has significant adverse effects,<sup>39</sup> and taking as few as 4-5 courses of OCS over 7 years' follow-up is associated with increased risk of serious long-term conditions including osteoporosis, pneumonia, cardiovascular disease, cataracts, renal impairment, diabetes and weight gain.<sup>40, 69</sup> Key strategies for reducing exacerbations include ICS-containing treatment (particularly as-needed-only ICS-formoterol or MART), managing risk factors, and providing a personalized written asthma action plan. The reduction in asthma exacerbations seen in many countries during the COVID-19 pandemic suggests that public health measures to reduce spread of SARS-CoV-2 infections (e.g., handwashing, social/physical distancing, mask-wearing) may be important in reducing transmission of other respiratory viruses.

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Patients at increased risk of asthma-related death should be identified, and reviewed more frequently. Factors include a history of requiring intubation and mechanical ventilation, hospitalization or emergency department (ED) visit for asthma in the previous year, not currently using or poorly adherent with ICS-containing therapy, over-use of SABAs,<sup>38</sup> a history of psychiatric disease or psychosocial problems, concomitant food allergy, and currently using or having recently stopped OCS (a marker of exacerbation severity) (GINA 2021, Box 4-1).

### **Written asthma action plans**

As part of asthma self-management, provide all patients with a written asthma action plan appropriate for their level of asthma control and health literacy, so they know how to recognize and respond to worsening asthma.<sup>19</sup> State when and how to change reliever and controller medications, use OCS if appropriate, and access medical care if symptoms fail to respond to treatment. Base the action plan on changes in symptoms or (only in adults) PEF.<sup>19</sup>

Advise patients who have a history of rapid deterioration to go to an acute care facility or see their doctor immediately if their asthma starts to worsen.

Action plan recommendations for responding to worsening asthma depend on the patient's usual therapy. Patients prescribed as-needed ICS-formoterol alone or in MART increase their as-needed doses as symptoms increase. Those on maintenance ICS-containing controller should increase to high dose temporarily (e.g., for 1-2 weeks) (see GINA 2021, Box 4-2).

*Rationale:* In a systematic review of self-management studies, action plans in which the ICS dose was at least doubled were associated with improved asthma outcomes and reduced healthcare utilization.<sup>71</sup> In some studies in adults and adolescents<sup>19, 72</sup> and pre-school children,<sup>73</sup> short-term higher-dose ICS reduced progression to a severe exacerbation and some

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found less impact on serum cortisol than OCS,<sup>74, 75</sup> but cost may be an issue. Given the shape of the ICS dose-response curve, the benefit of increasing maintenance ICS when asthma worsens may be greater when background adherence is lower. The timing of an increased ICS dose may be important: studies in adults in which the ICS dose was doubled 5-7 days after symptoms worsened found no reduction in severe exacerbations.<sup>76, 77</sup> In contrast, in maintenance and reliever therapy (MART), taking reliever doses of ICS-formoterol as soon as asthma symptoms occur, reduces the risk of progression to severe exacerbation.<sup>24, 25</sup>

### **Management of exacerbations in a primary care or acute care facility**

Assess exacerbation severity from mental state, degree of dyspnea, vital signs, oxygen saturation and lung function (PEF or spirometry), while starting treatment with repeated administration of SABA (in most patients, by pressurized metered dose inhaler and spacer) and controlled flow oxygen (sufficient flow to maintain oxygen saturation at 93-95% for adults; 94-98% for children 6-11 years), if available ([Figure 5](#)). Controlled oxygen therapy is associated with lower mortality and better outcomes than high concentration (100%) oxygen therapy.<sup>78-80</sup>

Arrange immediate transfer to an acute care facility if there are signs of severe exacerbation, or to intensive care, particularly if the patient is drowsy, confused, or has a silent chest. During transfer, give inhaled SABA and ipratropium bromide, controlled oxygen and systemic corticosteroids.

Repeated administration of albuterol (up to 4-10 puffs every 20 minutes for the first hour) is effective for rapidly reversing airflow limitation<sup>81</sup>. Avoid nebulization except for life-threatening asthma; delivery of rapid-acting beta<sub>2</sub>-agonist via a pressurized metered-dose inhaler and spacer or via a dry-powder inhaler is as effective in patients with moderately severe acute asthma,<sup>81, 82</sup> and avoids risk of disseminating infectious particles. Current

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evidence does not support the routine use of intravenous beta<sub>2</sub>-agonists in patients with severe asthma exacerbations.<sup>83</sup>

Start OCS early after presentation. For adults, give prednisolone 40-50 mg/day (or equivalent) for 5-7 days. For children, give prednisolone 1-2 mg/kg (maximum 40 mg) for 3-5 days.

Tapering is not needed if administered for <2 weeks.

Review response of symptoms, vital signs, oxygen saturation and lung function after 1 hour (or earlier if worsening). Give ipratropium bromide only for severe exacerbations. Consider intravenous magnesium sulfate for patients with severe exacerbations not responding to initial treatment.

Do not routinely request a chest radiography or routinely prescribe antibiotics for asthma exacerbations.

The decision whether to hospitalize should be based on the patient's clinical status, lung function, response to treatment, recent and past history of exacerbations, social support, and ability to manage at home.

*Rationale:* Currently, inhaled albuterol is the usual bronchodilator in acute asthma management. Similar efficacy and safety of formoterol in ED have been reported.<sup>84</sup> In one study, high-dose budesonide-formoterol had similar efficacy and safety to SABA in ED patients.<sup>85</sup>

### **Discharge management**

Before the patient goes home, arrange ongoing treatment. This should include starting ICS-containing controller treatment, preferably ICS-formoterol as MART ([Table 1](#), [Table E2](#), [downloadable resource](#)) to reduce the risk of another exacerbation, or stepping up the dose of existing maintenance treatment for 2-4 weeks. Advise patients to use reliever medication as

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needed, not regularly. Patients prescribed ICS-formoterol as their reliever should return to this after an ED presentation.

**Follow-up**

Arrange early follow-up after any exacerbation, regardless of where it was managed:

- Review the patient's symptom control and risk factors for further exacerbations.
- Prescribe/continue ICS-containing controller therapy (preferably MART with ICS-formoterol) to reduce the risk of further exacerbations. If already taking controller therapy, continue increased doses for 2-4 weeks.
- Provide a written asthma action plan and, where relevant, advice about avoiding exacerbation triggers.
- Check inhaler technique and adherence.

Asthma outcomes after an ED presentation for acute asthma are significantly improved by comprehensive intervention programs that include optimal controller management, inhaler technique, and elements of self-management education (self-monitoring, written action plan and regular review).<sup>86, 87</sup>

Referral for expert advice should be considered for patients who have been hospitalized for asthma, or who have repeat presentations to acute care settings. Follow-up by a specialist is associated with fewer subsequent ED visits or hospitalizations and better asthma control.<sup>87</sup>

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## Diagnosis and management of asthma in children 5 years and younger

### Diagnosis

Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral respiratory infections. Recognizing when this is the initial presentation of asthma is difficult. In young children with a history of wheezing, a diagnosis of asthma is more likely if they have any of the following:

- wheezing or coughing that occurs with exercise, laughing or crying, particularly in the absence of an apparent respiratory infection
- allergic sensitization, eczema, allergic rhinitis or food allergy, or asthma in first-degree relatives
- clinical improvement during 2-3 months of controller treatment, and worsening after cessation.

It is particularly important in this age group to consider and exclude alternative causes of wheeze, cough and breathlessness (GINA 2021, Box 6-3).

Important indications for referral of children  $\leq 5$  years for further diagnostic investigations include neonatal/very early onset of symptoms, failure to thrive, continuous wheezing, symptoms not associated with typical triggers (e.g., viral respiratory infections), or associated with vomiting, focal lung or cardiovascular signs, finger clubbing, hypoxemia outside the context of viral illness, or failure to respond to asthma medications.

### Initial treatment

The goals of asthma management in young children are to achieve good control of symptoms and maintain normal activity levels, and to minimize the risk of asthma exacerbations,



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impaired lung development and medication side-effects.

Wheezing episodes in young children should be treated initially with inhaled SABA, regardless of whether the diagnosis of asthma has been made. However, SABAs are generally ineffective for initial episodes of wheeze in children younger than 1 year with infectious bronchiolitis.

A trial of controller therapy (e.g., for 3 months) should be given if the symptom pattern suggests asthma, alternative diagnoses have been excluded, and respiratory symptoms are uncontrolled and/or wheezing episodes are frequent or severe (Figure 6). Response to treatment should be reviewed before deciding whether to continue it. If the response is absent or incomplete, reconsider alternative diagnoses.

It is important to discuss controller treatment choices with the child's parent/caregiver, to explain the relative benefits and risks of treatment, and the importance of maintaining normal activity levels for their child's physical and social development.

The choice of inhaler device should be based on the child's age and capability. The preferred device is a pressurized metered dose inhaler and spacer, with face mask for children younger than 3 years, and mouthpiece for most aged 3-5 years. Children should be switched from a face mask to mouthpiece as soon as they can demonstrate good technique.

Review the need for asthma treatment frequently, as asthma-like symptoms remit in many young children or may be markedly seasonal. Measure the child's height at least once every year.

**Asthma treatment steps for children  $\leq 5$  years**

**Step 1:** Provide inhaled SABA for relief of wheezing episodes. Need for SABA more than twice a week on average over 1 month indicates the need for a trial of controller medication.

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**Step 2:** The preferred option is regular daily low-dose ICS plus as-needed SABA, given for at least 3 months (see GINA 2021, Box 6-6 for ICS doses). Regular montelukast is less effective than low-dose ICS, and parents/caregivers should be counselled about potential neurobehavioral adverse effects, as in a boxed warning from the US Food and Drug Administration.<sup>88</sup>

**Step 3:** Before considering step-up to double the 'low' ICS dose, check for concomitant or alternative diagnoses, check and correct inhaler technique and adherence, and ask about risk factors such as exposure to allergen or tobacco smoke. ICS-LABA is not recommended in children <4 years old, as there are insufficient data about efficacy and safety.

**Step 4:** Refer the child for expert advice if symptoms and/or flare-ups persist, or at any time if side-effects of treatment are observed or suspected, or if there are doubts about diagnosis. See GINA 2021 Chapter 6 for details about other therapeutic options.

### **Managing exacerbations**

Early symptoms of exacerbations in young children may include increased symptoms, increased coughing (especially at night), lethargy or reduced exercise tolerance, impaired daily activities including feeding, and a poor response to reliever medication.

**Managing exacerbations at home:** Give a written asthma action plan to parents/caregivers of young children with asthma so they can recognize an impending exacerbation, start treatment, and identify when urgent hospital treatment is required. Initial treatment at home is with inhaled SABA, with review after 1 hour or earlier. If inhaled SABA is needed more often than 3-hourly or for >24 hours, treatment by a health provider is needed on the same day. Parents/caregivers should seek urgent medical care if the child is acutely distressed, lethargic, fails to respond to initial bronchodilator therapy, or is worsening, especially in

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children younger than 1 year.

*Rationale:* Most children with wheezing due to asthma respond to SABA. There is insufficient evidence for parent-initiated OCS in this age-group. Preemptive episodic parent-initiated high-dose nebulized ICS may reduce exacerbations in children with intermittent viral-triggered wheezing<sup>89</sup> but there are no long-term studies and a high risk of side-effects; it should only be considered if the clinician is confident that it will be used appropriately, and the child monitored closely for side-effects.

**Managing exacerbations in primary care or acute care facility:** Assess severity of the exacerbation while initiating treatment with SABA (2-6 puffs every 20 minutes for first hour) and controlled oxygen to maintain saturation 94-98%. Arrange immediate transfer to hospital if the child shows no response to inhaled SABA within 1-2 hours, is unable to speak or drink, has a respiratory rate >40/minute or is cyanosed, has oxygen saturation <92% on room air, or cannot be safely cared for at home.

For children attending an ED or admitted to hospital with asthma, consider systemic corticosteroids: oral prednisone/prednisolone 1-2 mg/kg/day for up to 5 days (maximum of 20 mg/day for children 0-2 years and 30 mg/day for children 3-5 years) or dexamethasone 0.6 mg/kg/day for 2 days.

**Follow-up:** Children who have experienced an asthma exacerbation are at risk of further exacerbations. Arrange follow-up within 1-2 days of an exacerbation and again 1-2 months later to identify modifiable risk factors and exacerbation triggers, optimize ongoing asthma management, and check inhaler technique and adherence.

## Primary prevention of asthma in children

The development and persistence of asthma are driven by gene-environment interactions. For children, a ‘window of opportunity’ to prevent asthma exists in utero and in early life, but intervention studies are limited. Current advice and recommendations for preventing asthma in children, based on high-quality evidence<sup>90, 91</sup> or consensus, include the following:

- Avoid exposure to environmental tobacco smoke during pregnancy and after birth.
- Encourage vaginal delivery where possible.
- Where possible, avoid the use of acetaminophen and broad-spectrum antibiotics during the first year of life.
- Identification and correction of Vitamin D insufficiency in women with asthma who are pregnant, or planning pregnancy, may reduce the risk of early life wheezing episodes, but not asthma.
- Allergen avoidance strategies directed at a single allergen have not been effective in preventing asthma. Multifaceted strategies may be effective, but the essential components have not been identified.

Breast-feeding is advised for its general health benefits.

## Implementation of asthma management strategies into health systems

To improve asthma care and patient outcomes, evidence-based recommendations must be disseminated and implemented nationally and locally, and integrated into health systems and clinical practice.<sup>92</sup> Implementation requires an evidence-based strategy involving professional groups and stakeholders and considering local cultural and socioeconomic conditions. Cost-

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effectiveness of implementation programs should be assessed so a decision can be made to pursue or modify them. Local adaptation and implementation of asthma care strategies are aided by purpose-developed tools.<sup>92</sup>

### **Asthma management in low-resource settings**

GINA 2021 is a global strategy relevant to the care of all children, adolescents and adults with asthma, wherever they live. Most of the global burden of asthma morbidity and mortality occurs in low-income and middle-income countries,<sup>1, 93</sup> due to lack of necessary resources for effective long-term asthma care.<sup>1, 93, 94</sup> GINA has identified ongoing lack of access to ICS as a serious concern<sup>4</sup>, especially as they can be produced at low cost. The safest and most effective approach to asthma treatment in adolescents and adults, which also avoids the consequences of starting treatment with SABA alone, depends on access to ICS-formoterol across all asthma severity levels.<sup>4</sup> However, despite listing of budesonide-formoterol on WHO's Essential Medicines List,<sup>95</sup> affordable access is very limited in many low-resource settings.<sup>1, 4, 93, 94, 96</sup> The urgent need to ensure access to affordable quality-assured inhaled asthma medications as part of universal health coverage must now be prioritized by all relevant stakeholders, particularly manufacturers of inhalers on the WHO Essential Medicines List.<sup>95</sup>

### **Topics requiring further research**

In addition to ongoing evidence reviews across the whole asthma strategy, GINA plans to review the following topics:

- the definition of mild asthma

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- assessment of symptom control in patients whose reliever is ICS-formoterol
- subcutaneous and sublingual allergen immunotherapy
- the diagnosis and management of asthma in pre-school children
- the use of digital tools and communication in asthma management
- management of asthma in low- and middle-income countries.

GINA also plans to develop a pocket guide for severe asthma in children 6-11 years. COVID-19 advice on the GINA website will be updated as new evidence emerges.

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## References

1. Global Asthma Network. *The global asthma report 2018*. Auckland, New Zealand: Global Asthma Network; 2018.
2. National Heart Lung and Blood Institute National Asthma Education and Prevention Program, World Health Organization. *Global Initiative for Asthma. National Institutes of Health publication no 95-3659*. Bethesda: National Institutes of Health; 1995.
3. Global Initiative for Asthma. Methodology. [Web page]: GINA; 2021 [cited 2021 September]. Web page]. Available from: <https://ginasthma.org/about-us/methodology>.
4. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. GINA; 2021 [cited 2021 October]. Available from: [www.ginasthma.org/reports](http://www.ginasthma.org/reports).
5. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemièrre C, Field SK, McIvor RA, Hernandez P, Mayers I, Mulpuru S, Alvarez GG, Pakhale S, Mallick R, Boulet LP. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* 2017; 317: 269-279.
6. Reddel H, Taylor D, Bateman E, Boulet L, Boushey H, Busse W, Casale T, Chanez P, Enright P, Gibson P, de Jongste J, Kerstjens H, Lazarus S, Levy M, O'Byrne P, Partridge M, Pavord I, Sears M, Sterk P, Stoloff S, Sullivan S, Szeffler S, Thomas M, Wenzel S, American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180: 59-99.
7. Schatz M, Kosinski M, Yarlus AS, Hanlon J, Watson M, Jhingran P. The minimally important difference of the Asthma Control Test. *J Allergy Clin Immunol* 2009; 124: 719-723.
8. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005; 99: 553-558.



## GINA 2021 Executive summary

9. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, Devillier P, Didier A, Leroyer C, Marguet C, Martinat Y, Piquet J, Raheison C, Serrier P, Tillie-Leblond I, Tonnel AB, Tunon de Lara M, Humbert M. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007; 62: 591-604.
10. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretive strategies for lung function tests. *Eur Respir J* 2005; 26: 948-968.
11. Barnes PJ, Szefler SJ, Reddel HK, Chipps BE. Symptoms and perception of airway obstruction in asthmatic patients: clinical implications for use of reliever medications. *J Allergy Clin Immunol* 2019; 144: 1180-1186.
12. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness R, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-373.
13. Global Initiative for Asthma. Difficult-to-treat and severe asthma in adolescent and adult patients. Diagnosis and management. A GINA pocket guide for health professionals. Version 3. April 2021. GINA; 2021 [cited 2021 September]. Available from: [www.ginasthma.org/reports](http://www.ginasthma.org/reports).
14. Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017; 389: 157-166.
15. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Pavord ID, Williams M, Weatherall M. Controlled trial of budesonide-formoterol as needed for mild asthma. *N Engl J Med* 2019; 380: 2020-2030.

## GINA 2021 Executive summary

16. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, Corin A, Sparks J, Hall D, Sabbagh D, Mane S, Vohlidkova A, Martindale J, Williams M, Shirtcliffe P, Holliday M, Weatherall M, Beasley R. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019; 394: 919-928.
17. Agusti A, Bel E, Thomas M, Vogelmeier C, Brusselle G, Holgate S, Humbert M, Jones P, Gibson PG, Vestbo J, Beasley R, Pavord ID. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410-419.
18. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM, START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071-1076.
19. Pinnock H, Parke HL, Panagioti M, Daines L, Pearce G, Epiphaniou E, Bower P, Sheikh A, Griffiths CJ, Taylor SJ. Systematic meta-review of supported self-management for asthma: a healthcare perspective. *BMC Med* 2017; 15: 64.
20. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002; 57: 880-884.
21. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865-1876.
22. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000; 343: 332-336.
23. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009; 179: 19-24.

## GINA 2021 Executive summary

24. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE, Baker WL. 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.
25. Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013; Issue 4.
26. Parsons J, Hallstrand T, Mastrorarde J, Kaminsky D, Rundell K, Hull J, Storms W, Weiler J, Cheek F, Wilson K, Anderson SD, American Thoracic Society Subcommittee on Exercise-induced Bronchoconstriction. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013; 187: 1016-1027.
27. Lazarinis N, Jorgensen L, Ekstrom T, Bjermer L, Dahlen B, Pullerits T, Hedlin G, Carlsen KH, Larsson K. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014; 69: 130-136.
28. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet LP. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.
29. Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. *BMJ Open* 2017; 7: e016688.
30. Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. *Respir Med* 2000; 94: 767-771.

## GINA 2021 Executive summary

31. Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993; 342: 833-837.
32. Pavord ID, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, Harrison T, Houghton C, Oldfield K, Papi A, Williams M, Weatherall M, Beasley R, Novel SST. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med* 2020; 8: 671-680.
33. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Siwek-Posluszna A, FitzGerald JM. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877-1887.
34. O'Byrne P, FitzGerald JM, Bateman ED, Barnes PJ, Zheng J, Gustafson P, Lamarca R, Puu M, Keen C, Alagappan V, Reddel H. A single day of higher as-needed budesonide/formoterol use reduces short-term risk of a severe exacerbation in patients with mild asthma: a post hoc analysis of SYGMA 1. *Lancet Respir Med* 2021; 9: 149-158.
35. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, Rabe KF. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. *Respir Res* 2012; 13: 59.
36. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aquilar NE, Carlsheimer A. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007; 101: 2437-2446.
37. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting beta-agonist use and its ability to predict future asthma-related outcomes. *Ann Allergy Asthma Immunol* 2012; 109: 403-407.

## GINA 2021 Executive summary

38. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting  $\beta$ 2-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.
39. Waljee AK, Rogers MA, Lin P, Singal AG, Stein JD, Marks RM, Ayanian JZ, Nallamothu BK. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017; 357: j1415.
40. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, Tran TN. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018; 11: 193-204.
41. Bärnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015; 60: 455-468.
42. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; 356: 2040-2052.
43. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M, Cherniack RM, Chinchilli VM, Craig T, Denlinger L, DiMango EA, Engle LL, Fahy JV, Grant A, Israel E, Jarjour N, Kazani SD, Kraft M, Kunselman SJ, Lazarus SC, Lemanske RF, Lugogo N, Martin RJ, Meyers DA, Moore WC, Pascual R, Peters SP, Ramsdell J, Sorkness CA, Sutherland RE, Szeffler SJ, Wasserman SI, Walter MJ, Wechsler ME, Boushey HA, Asthma Clinical Research Network of the National Heart Lung and Blood Institute. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012; 308: 987-997.

## GINA 2021 Executive summary

44. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF, Mauger DT, Strunk RC, Szeffler S, Zeiger RS, Bacharier LB, Bade E, Covar RA, Friedman NJ, Guilbert TW, Heidarian-Raissy H, Kelly HW, Malka-Rais J, Mellon MH, Sorkness CA, Taussig L. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 650-657.
45. Sumino K, Bacharier LB, Taylor J, Chadwick-Mansker K, Curtis V, Nash A, Jackson-Triggs S, Moen J, Schechtman KB, Garbutt J, Castro M. A pragmatic trial of symptom-based inhaled corticosteroid use in African-American children with mild asthma. *J Allergy Clin Immunol Pract* 2020; 8: 176-185.e172.
46. Demoly P, Louis R, Søres-Petersen U, Naya I, Carlsheimer A, Worth H, Almeida J, Sears MR. Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med* 2009; 103: 1623-1632.
47. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, Naya I, Price D. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005; 26: 819-828.
48. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R, The SMART Study Group. Efficacy and safety of maintenance and reliever combination budesonide-formoterol in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32-42.
49. Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, Fabbri LM, Rabe KF. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013; 1: 23-31.
50. Bateman ED, Harrison TW, Quirce S, Reddel HK, Buhl R, Humbert M, Jenkins CR, Peterson S, Ostlund O, O'Byrne PM, Sears MR, Eriksson GS. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res* 2011; 12: 38.

## GINA 2021 Executive summary

51. Jorup C, Lythgoe D, Bisgaard H. Budesonide/formoterol maintenance and reliever therapy in adolescent patients with asthma. *Eur Respir J* 2018; 51.
52. Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006; 130: 1733-1743.
53. Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, Liu AH, Mitchell H, Kral KM, Raphiou IH, Prillaman BA, Buaron KS, Yun Kirby S, Pascoe SJ. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med* 2016; 375: 840-849.
54. Murphy VE, Gibson PG. Asthma in pregnancy. *Clin Chest Med* 2011; 32: 93-110.
55. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management and Prevention of COPD. 2021 Report. GOLD; 2021 [cited 2021 September]. Available from: <https://goldcopd.org/>.
56. Gershon AS, Campitelli MA, Croxford R, Stanbrook MB, To T, Upshur R, Stephenson AL, Stukel TA. Combination long-acting  $\beta$ -agonists and inhaled corticosteroids compared with long-acting  $\beta$ -agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA* 2014; 312: 1114-1121.
57. Suissa S, Ernst P. Observational studies of inhaled corticosteroid effectiveness in COPD: lessons learned. *Chest* 2018; 154: 257-265.
58. Kendzerska T, Aaron SD, To T, Licskai C, Stanbrook M, Vozoris NT, Hogan ME, Tan WC, Bourbeau J, Gershon AS. Effectiveness and safety of inhaled corticosteroids in older individuals with chronic obstructive pulmonary disease and/or asthma. A population study. *Ann Am Thorac Soc* 2019; 16: 1252-1262.
59. Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015; 135: 896-902.
60. Foster JM, McDonald VM, Guo M, Reddel HK. "I have lost in every facet of my life": the hidden burden of severe asthma. *Eur Respir J* 2017; 50: 1700765.

## GINA 2021 Executive summary

61. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P, Iridium trial investigators. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med* 2020; 8: 1000-1012.
62. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet* 2019; 394: 1737-1749.
63. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med* 2021; 9: 69-84.
64. Casale TB, Aalbers R, Bleecker ER, Meltzer EO, Zaremba-Pechmann L, de la Hoz A, Kerstjens HAM. Tiotropium Respimat(R) add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. *Respir Med* 2019; 158: 97-109.
65. Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. 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.
66. Hiles SA, McDonald VM, Guilhermino M, Brusselle GG, Gibson PG. Does maintenance azithromycin reduce asthma exacerbations? An individual participant data meta-analysis. *Eur Respir J* 2019; 54: 1901381.



## GINA 2021 Executive summary

67. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2017; 8: Cd005603.
68. Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, Gaga M, Kellermeier L, Khurana S, Knight S, McDonald VM, Morgan RL, Ortega VE, Rigau D, Subbarao P, Tonia T, Adcock IM, Bleecker ER, Brightling C, Boulet LP, Cabana M, Castro M, Chanez P, Custovic A, Djukanovic R, Frey U, Frankemolle B, Gibson P, Hamerlijck D, Jarjour N, Konno S, Shen H, Vitary C, Bush A. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2020; 55: 1900588.
69. Lefebvre P, Duh MS, Lafeuille MH, Gozalo L, Desai U, Robitaille MN, Albers F, Yancey S, Ortega H, Forshag M, Lin X, Dalal AA. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015; 136: 1488-1495.
70. Blaiss MS, Nathan RA, Stoloff SW, Meltzer EO, Murphy KR, Doherty DE. Patient and physician asthma deterioration terminology: results from the 2009 Asthma Insight and Management survey. *Allergy Asthma Proc* 2012; 33: 47-53.
71. Gibson P, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax* 2004; 59: 94-99.
72. McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, Pavord I, Price D, Duley L, Thomas M, Bradshaw L, Higgins B, Haydock R, Mitchell E, Devereux G, Harrison T. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018; 378: 902-910.
73. Ducharme FM, Lemire C, Noya FJ, Davis GM, Alos N, Leblond H, Savdie C, Collet JP, Khomenko L, Rivard G, Platt RW. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009; 360: 339-353.
74. van den Berge M, Arshad SH, Ind PW, Magnussen H, Hamelmann E, Kanniess F, Postma DS. Similar efficacy of ciclesonide versus prednisolone to treat asthma worsening after steroid tapering. *Respir Med* 2009; 103: 1216-1223.

## GINA 2021 Executive summary

75. Wilson AM, Lipworth BJ. Short-term dose-response relationships for the relative systemic effects of oral prednisolone and inhaled fluticasone in asthmatic adults. *Br J Clin Pharmacol* 1999; 48: 579-585.
76. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004; 59: 550-556.
77. Harrison TW, Osborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004; 363: 271-275.
78. Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, Weatherall M, Beasley R. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. *Thorax* 2011; 66: 937-941.
79. Patel B, Khine H, Shah A, Sung D, Medar S, Singer L. Randomized clinical trial of high concentration versus titrated oxygen use in pediatric asthma. *Pediatr Pulmonol* 2019; 54: 970-976.
80. Siemieniuk RAC, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccia PM, Karanicolas PJ, Farhoumand PD, Siemieniuk JLK, Satia I, Irusen EM, Refaat MM, Mikita JS, Smith M, Cohen DN, Vandvik PO, Agoritsas T, Lytvyn L, Guyatt GH. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018; 363: k4169.
81. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2013; Issue 9.
82. Selroos O. Dry-powder inhalers in acute asthma. *Ther Deliv* 2014; 5: 69-81.
83. Travers AH, Milan SJ, Jones AP, Camargo CA, Rowe BH. Addition of intravenous beta<sub>2</sub>-agonists to inhaled beta<sub>2</sub>-agonists for acute asthma. *Cochrane Database Syst Rev* 2012; Issue 12: CD010179.
84. Rodrigo G, Neffen H, Colodenco F, Castro-Rodriguez J. Formoterol for acute asthma in the emergency department: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2010; 104: 247-252.

## GINA 2021 Executive summary

85. Balanag VM, Yunus F, Yang PC, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006; 19: 139-147.
86. Gibson PG, Powell H, Wilson AJ, Abramson MJ, Haywood P, Bauman A, Hensley MJ, Walters EH, Roberts JLL. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev* 2003; Issue 3: CD001117.
87. Schatz M, Rachelefsky G, Krishnan J. Follow-up after acute asthma episodes: what improves future outcomes? *Proc Am Thorac Soc* 2009; 6: 386-393.
88. US 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. [Web page]: FDA; 2020 [cited 2021 September]. 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>.
89. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics* 2016; 137.
90. Brożek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, van Wijk RG, Ohta K, Zuberbier T, Schünemann HJ. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010; 126: 466-476.
91. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015; 386: 1075-1085.
92. Boulet LP, FitzGerald JM, Levy ML, Cruz AA, Pedersen S, Haahtela T, Bateman ED. A guide to the translation of the Global Initiative for Asthma (GINA) strategy into improved care. *Eur Respir J* 2012; 39: 1220-1229.

## GINA 2021 Executive summary

93. Meghji J, Mortimer K, Agusti A, Allwood BW, Asher I, Bateman ED, Bissell K, Bolton CE, Bush A, Celli B, Chiang CY, Cruz AA, Dinh-Xuan AT, El Sony A, Fong KM, Fujiwara PI, Gaga M, Garcia-Marcos L, Halpin DMG, Hurst JR, Jayasooriya S, Kumar A, Lopez-Varela MV, Masekela R, Mbatchou Ngahane BH, Montes de Oca M, Pearce N, Reddel HK, Salvi S, Singh SJ, Varghese C, Vogelmeier CF, Walker P, Zar HJ, Marks GB. Improving lung health in low-income and middle-income countries: from challenges to solutions. *Lancet* 2021; 397: 928-940.
94. Asher I, Bissell K, Chiang CY, El Sony A, Ellwood P, García-Marcos L, Marks GB, Mortimer K, Pearce N, Strachan D. Calling time on asthma deaths in tropical regions-how much longer must people wait for essential medicines? *Lancet Respir Med* 2019; 7: 13-15.
95. World Health Organization. WHO Model Lists of Essential Medicines. WHO; 2021 [cited 2021 September]. Available from: <https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists>.
96. Sanyang B, Jagne E, Sefa N, Touray S. Availability, cost, and affordability of asthma and chronic obstructive pulmonary disease medications in The Gambia. 2021; 2: 33-41.

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[Figure legends]

**Figure 1. GINA assessment of asthma control in adults, adolescents and children 6–11 years**

Source: GINA 2021 (Box 2-2)<sup>4</sup>

For a fully referenced version of this table, please see GINA strategy report 2021.

BD: bronchodilator; FEV<sub>1</sub>: forced expiratory volume in 1 second; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; OCS: oral corticosteroid; P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, itraconazole; SABA: short-acting beta<sub>2</sub>-agonist.

\*Based on SABA (as-needed ICS-formoterol reliever not included); excludes reliever taken before exercise. For children 6-11 years, see also GINA 2021, Box 2-3). For specific risk reduction strategies, see GINA 2021, Box 3-8.

†‘Independent’ risk factors are those that are significant after adjustment for the level of symptom control.

**Figure 2. Personalized asthma management cycle of care**

Source: GINA 2021 (Box 3-2)<sup>4</sup>

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**Figure 3. Personalized management for adults and adolescents to control symptoms and minimize risk**

Source: GINA 2021 (Box 3-5A)<sup>4</sup>

HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist;

LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta<sub>2</sub>-agonist; SLIT: sublingual immunotherapy. For ICS doses, see GINA 2021, Box 3-6.

**Figure 4. Personalized management for children 6–11 years to control symptoms and minimize future risk**

Source: GINA 2021 (Box 3-5B)<sup>4</sup>

BUD-FORM: budesonide-formoterol; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist; LTRA: leukotriene receptor antagonist; MART: maintenance and reliever therapy with ICS-formoterol; OCS: oral corticosteroids; SABA: short-acting beta<sub>2</sub>-agonist. For ICS doses for children, see GINA 2021, Box 3-6. For MART doses, see [Table E2](#) and [downloadable resource](#).

**Figure 5. Management of asthma exacerbations in primary care (adults, adolescents, children 6-11 years)**

Source: GINA 2021 (Box 4-3)<sup>4</sup>

O<sub>2</sub>: oxygen; PEF: peak expiratory flow; SABA: short-acting beta<sub>2</sub>-agonist (doses are for

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albuterol).

**Figure 6. Personalized management of asthma in children 5 years and younger**

Source: GINA 2021 (Box 6-5)<sup>4</sup>

ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonist; SABA: short-acting  
beta<sub>2</sub> agonist

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**Table 1. Differences between current asthma treatment regimens containing an anti-inflammatory reliever (AIR)**

	<b>Anti-inflammatory reliever (AIR) therapy alone</b> (GINA Steps 1–2)	<b>Maintenance and reliever therapy (MART*)</b> (GINA Steps 3, 4, 5)
Definition	Combination ICS-formoterol taken as needed for symptom relief <sup>†</sup> , without maintenance therapy <i>or, if not available, low-dose ICS taken whenever SABA is taken for symptom relief</i>	Daily maintenance ICS-formoterol <b>PLUS</b> Low-dose ICS-formoterol taken as needed for symptom relief <sup>†</sup>
Indications	<b>Mild asthma: GINA Steps 1–2</b>	<b>Moderate-to-severe asthma: GINA Steps 3, 4 and 5</b>
Explanation	Whenever symptom relief is needed, the patient takes an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA), without daily maintenance treatment. <i>Or, if ICS-formoterol is not available, they take a low dose of ICS whenever SABA is taken</i>	The patient takes <b>regular daily maintenance</b> controller treatment with low-dose (Step 3) or medium dose (Step 4) combination ICS-formoterol. <b>PLUS</b> Whenever needed for symptom relief, the patient uses an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA).
Medications and age-	Budesonide-formoterol (≥12 years) <i>There have been smaller studies with</i>	Budesonide-formoterol (ages ≥4 years) or beclometasone-formoterol (adults)



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groups studied	<i>beclometasone-albuterol in combination or separate inhalers in adults <math>\geq 18</math> years, adolescents and children <math>\geq 4</math> years.</i>	$\geq 18$ years)
Rationale	<p>In patients with mild asthma, as-needed-only budesonide-formoterol reduced severe exacerbations by <math>\geq 60\%</math> compared with SABA alone, with similar symptom control and lung function as maintenance ICS plus as-needed SABA.</p> <p><i>With as-needed-only ICS+SABA in patients with mild asthma, some studies showed fewer exacerbations than SABA alone; other studies showed similar outcomes to physician-adjusted ICS treatment.</i></p>	<p>In moderate-severe asthma, maintenance and reliever therapy with ICS-formoterol reduced severe exacerbations compared with same or high dose ICS or ICS-LABA plus as-needed SABA, with similar symptom control and lung function.</p> <p><i>There have been no studies with ICS+SABA used as both maintenance and reliever therapy, and some evidence suggests that taking ICS+SABA regularly may increase exacerbation risk.</i></p>

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AIR: anti-inflammatory reliever, a term used for reliever inhalers that contain a combination of an ICS with either formoterol or albuterol; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub> agonist; MART: maintenance and reliever therapy; SABA: short-acting beta<sub>2</sub>-agonist

\* Also called single-inhaler maintenance and reliever therapy (SMART)

† For dosage details, see [Table E2](#) and [downloadable resource](#) in the online data supplement

ICS-formoterol contains a combination of an inhaled corticosteroid (e.g., budesonide or

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beclometasone) and formoterol, a rapid-onset long-acting beta<sub>2</sub>-agonist that, for most patients, relieves symptoms and bronchoconstriction as quickly as a SABA. When

**budesonide-formoterol** or **beclometasone-formoterol** are used as needed, a single inhalation is taken for symptom relief. If symptoms persist after a few minutes, an additional inhalation can be taken, but no more than 6 inhalations should be taken on a single occasion (4 inhalations of budesonide-formoterol for children 4–11 years). The maximum total dose (reliever inhalations plus maintenance inhalations, if used) that can be used temporarily in a single day is 12 inhalations of budesonide-formoterol for adults/adolescents (total 8 inhalations for children 4–11 years) and total 8 inhalations of beclometasone-formoterol for adults. If patients need more than this, they should seek medical help the same day.

**Other ICS-formoterol formulations** (e.g., mometasone-formoterol, fluticasone propionate-formoterol) have not been studied as anti-inflammatory relievers, either alone or in MART, but could be substituted if budesonide-formoterol or beclometasone-formoterol is not available. Before prescribing any inhaler, ensure that the patient can use it correctly.

The recommended maximum doses refer to the maximum total dose that can be taken temporarily on any single day, not the expected or desirable average use. In clinical trials of as-needed budesonide-formoterol in adults and adolescents with mild asthma, patients used an average of only 3-4 inhalations per week of low-dose budesonide-formoterol, and <0.1% of patients took >8 inhalations of budesonide-formoterol on more than 1 day during the 12 months of treatment.<sup>21, 33</sup>

For all patients prescribed as-needed-only ICS-formoterol or MART, *average* frequency of as-needed use of ICS-formoterol over the previous 4 weeks should be reviewed at each visit as part of the assessment of their treatment needs, especially when considering the need for maintenance treatment.

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Combinations of ICS with non-formoterol long-acting beta<sub>2</sub>-agonists (LABA), or combinations of ICS, LABA and long-acting muscarinic antagonists (LAMA), should not be used as-needed; they are recommended only for maintenance treatment. For patients using a **non-formoterol ICS-LABA** (with or without a LAMA), the appropriate reliever is SABA.

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**Figure 1. GINA assessment of asthma control in adults, adolescents and children 6–11 years**

A. Asthma symptom control		Level of asthma symptom control			
In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled	
• Daytime asthma symptoms more than twice/week?	Yes <input type="checkbox"/> No <input type="checkbox"/>	None of these	1–2 of these	3–4 of these	
• Any night waking due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>				
• SABA reliever for symptoms more than twice/week?*	Yes <input type="checkbox"/> No <input type="checkbox"/>				
• Any activity limitation due to asthma?	Yes <input type="checkbox"/> No <input type="checkbox"/>				
B. Risk factors for poor asthma outcomes					
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations.					
Measure FEV <sub>1</sub> at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment.					
<b>Having uncontrolled asthma symptoms is an important risk factor for exacerbations.</b>					
Additional <b>potentially modifiable risk factors for flare-ups (exacerbations)</b> , even in patients with few symptoms† include:					
<ul style="list-style-type: none"> <li>• <b>Medications:</b> high SABA use (associated with increased risk of exacerbations and mortality particularly if ≥1 x 200-dose canister per month); inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique</li> <li>• <b>Other medical conditions:</b> obesity; chronic rhinosinusitis; GERD; confirmed food allergy; pregnancy</li> <li>• <b>Exposures:</b> smoking; allergen exposure if sensitized; air pollution</li> <li>• <b>Context:</b> major psychological or socioeconomic problems</li> <li>• <b>Lung function:</b> low FEV<sub>1</sub>, especially &lt;60% predicted; high BD reversibility</li> <li>• <b>Other tests</b> in patients with Type 2 inflammation: blood eosinophils; elevated FeNO (in adults with allergic asthma taking ICS)</li> </ul>				<p><b>Having any of these risk factors increases the patient's risk of exacerbations even if they have few asthma symptoms</b></p>	
Other major independent risk factors for flare-ups (exacerbations)					
<ul style="list-style-type: none"> <li>• Ever intubated or in intensive care unit for asthma</li> <li>• ≥1 severe exacerbation in last 12 months</li> </ul>					
Risk factors for developing persistent airflow limitation					
<ul style="list-style-type: none"> <li>• History: preterm birth, low birth weight and greater infant weight gain; chronic mucus hypersecretion</li> <li>• Medications: lack of ICS treatment in patients who had a severe exacerbation</li> <li>• Exposures: tobacco smoke; noxious chemicals; occupational exposures</li> <li>• Investigations: low initial FEV<sub>1</sub>; sputum or blood eosinophilia</li> </ul>					
Risk factors for medication side-effects					
<ul style="list-style-type: none"> <li>• Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors</li> <li>• Local: high dose or potent ICS; poor inhaler technique</li> </ul>					

Figure footnotes

Figure 2. Personalized asthma management cycle of care

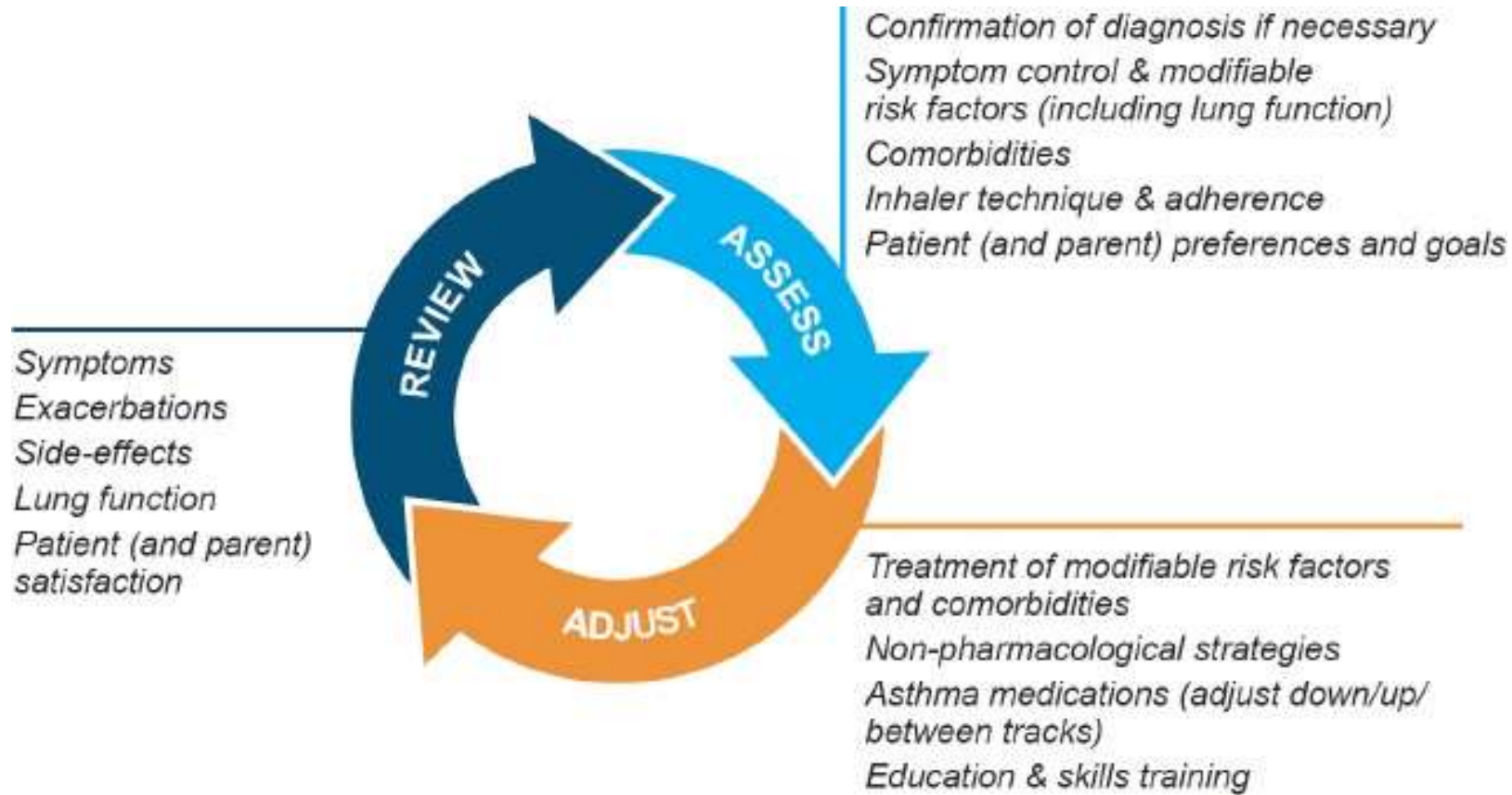
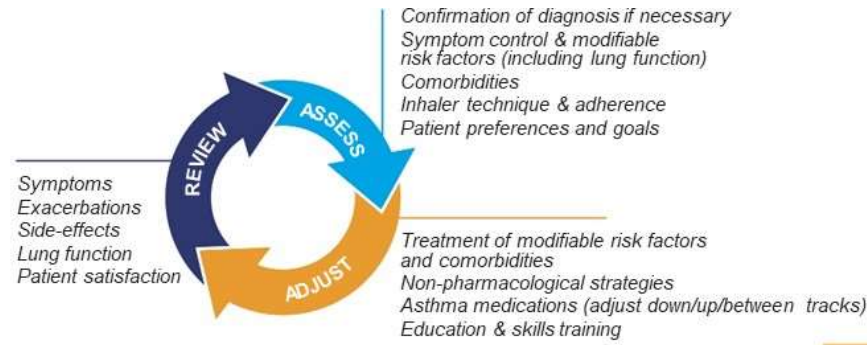


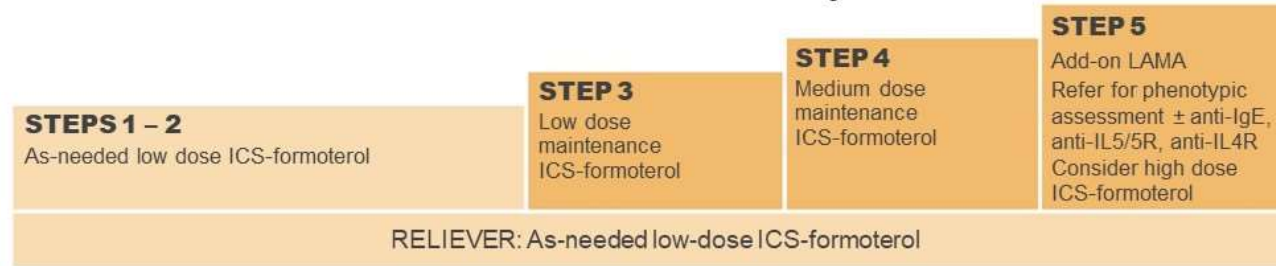
Figure footnotes

Figure 3. Personalized management for adults and adolescents to control symptoms and minimize risk

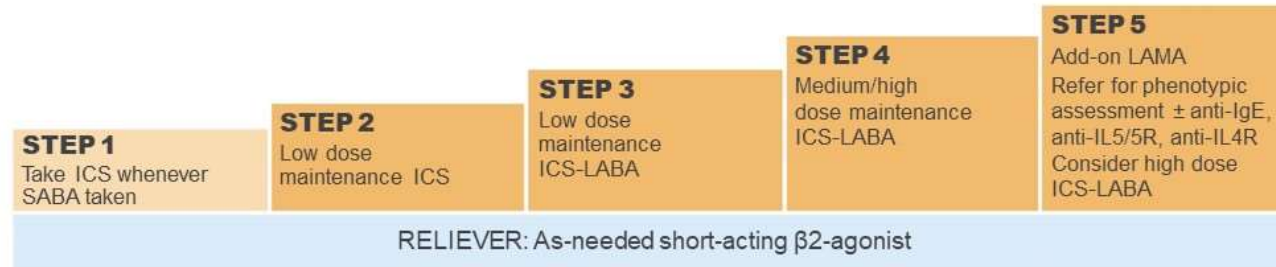
**Adults & adolescents  
12+ years**  
**Personalized asthma management**  
Assess, Adjust, Review  
for individual patient needs



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



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



Other controller options for either track

	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	Medium dose ICS, or add LTRA, or add HDM SLIT	Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS	Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects
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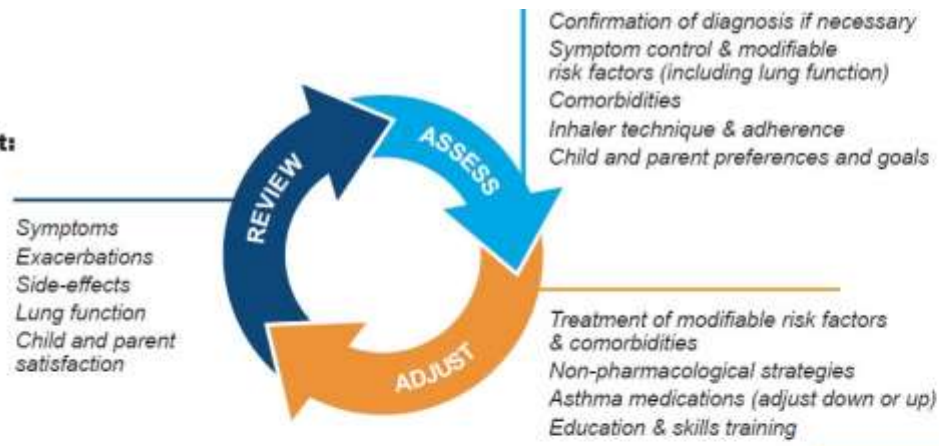
Figure footnotes

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Figure 4. Personalized management for children 6–11 years to control symptoms and minimize future risk

**Children 6-11 years**

**Personalized asthma management:**  
Assess, Adjust, Review



**Asthma medication options:**  
Adjust treatment up and down for individual child's needs

**PREFERRED CONTROLLER**  
to prevent exacerbations and control symptoms.

Other controller options

**RELIEVER**

	<b>STEP 1</b> Low dose ICS taken whenever SABA taken.	<b>STEP 2</b> Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	<b>STEP 3</b> Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	<b>STEP 4</b> Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	<b>STEP 5</b> Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken	Low dose ICS + LTRA	Add tiotropium or add LTRA	Add-on anti-IL5, or add-on low dose OCS, but consider side-effects	
As-needed short-acting beta2-agonist (or ICS-formoterol reliever for MART as above)					

\*Very low dose: BUD-FORM 100/6 mcg

†Low dose: BUD-FORM 200/6 mcg (metered doses).

Figure footnotes

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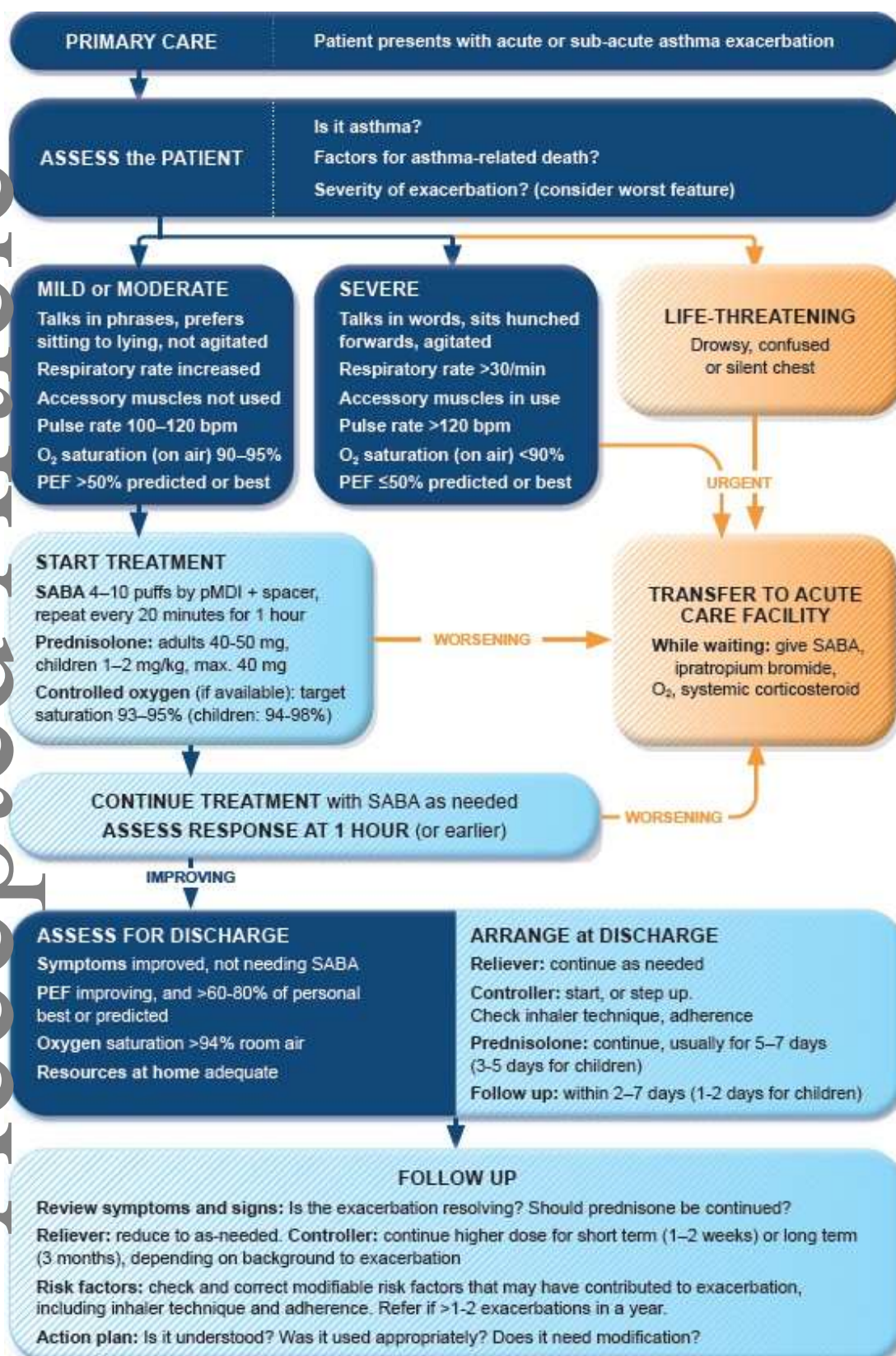
**Figure 5. Management of asthma exacerbations in primary care (adults, adolescents, children 6–11 years)**

Figure footnotes



Figure 6. Personalized management of asthma in children 5 years and younger

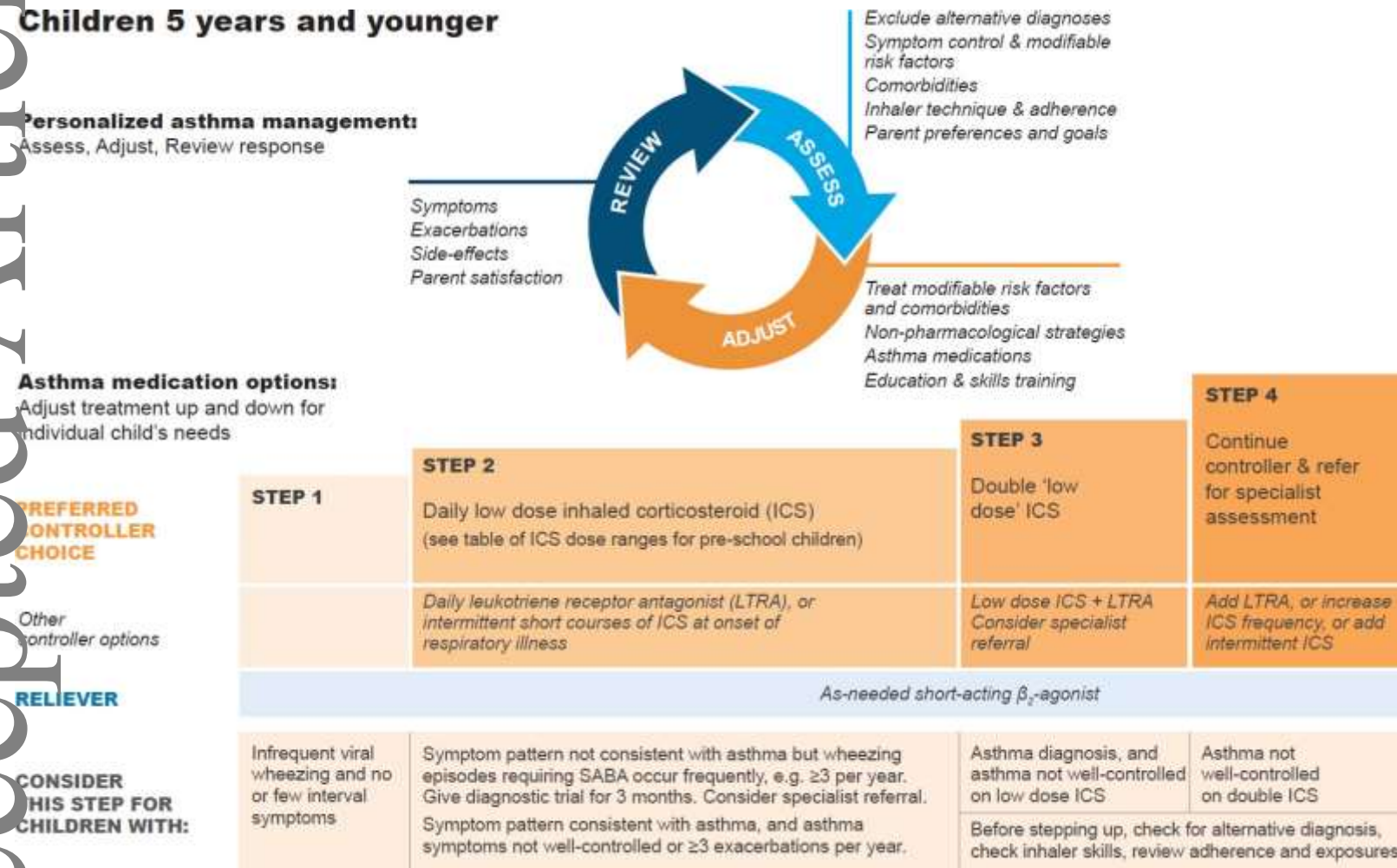


Figure footnotes

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## Supplementary information

### *Global Initiative for Asthma (GINA) Strategy 2021 – Executive summary and rationale for key changes*

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**Table E1. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years**

<b>1. History of variable respiratory symptoms</b>	
<i>Feature</i>	<i>Symptoms/features that support the diagnosis of asthma</i>
Wheeze, shortness of breath, chest tightness and cough (descriptors may vary between cultures and by age group)	<p>More than one type of respiratory symptom. In adults, isolated cough is seldom due to asthma.</p> <p>Symptoms occur variably over time and vary in intensity</p> <p>Symptoms often worse at night or on waking</p> <p>Symptoms often triggered by exercise, laughter, allergens, cold air</p> <p>Symptoms often appear or worsen with viral respiratory infections</p>
<b>2. Confirmed variable expiratory airflow limitation</b>	
<i>Feature</i>	<i>Considerations, definitions, criteria</i>
<b>2.1 Documented* expiratory airflow limitation</b>	At a time when FEV <sub>1</sub> is reduced, confirm that FEV <sub>1</sub> /FVC is reduced compared with the lower limit of normal (usually >0.75–0.80 in adults, >0.90 in children).
<b>AND</b>	
<b>2.2 Documented* excessive variability in lung function (one or more of the following):</b>	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
Positive bronchodilator (BD) responsiveness test (reversibility) <sup>†</sup>	<p><b>Adults:</b> increase in FEV<sub>1</sub> &gt;12% and &gt;200 ml (greater confidence if increase &gt;15% and &gt;400 ml)</p> <p><b>Children:</b> increase in FEV<sub>1</sub> &gt;12% predicted</p> <p>Measure change 10-15 minutes after 200–400 mcg albuterol or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: withhold SABA for ≥4 hours, twice-daily LABA 24 hours, once-daily LABA 36 hours.</p>
Excessive variability in twice-daily PEF <sup>§</sup> over 2 weeks	<p><b>Adults:</b> average daily diurnal PEF variability &gt;10%<sup>‡</sup></p> <p><b>Children:</b> average daily diurnal PEF variability &gt;13%<sup>‡</sup></p>
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	<b>Adults:</b> increase in FEV <sub>1</sub> by >12% and >200 ml (or PEF <sup>§</sup> by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test	<p><b>Adults:</b> fall in FEV<sub>1</sub> of &gt;10% and &gt;200 ml from baseline</p> <p><b>Children:</b> fall in FEV<sub>1</sub> of &gt;12% predicted, or PEF &gt;15%</p>
Positive bronchial challenge test (usually only for adults)	Fall in FEV <sub>1</sub> from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits (good specificity but poor sensitivity)	<p><b>Adults:</b> variation in FEV<sub>1</sub> of &gt;12% and &gt;200 ml between visits, outside of respiratory infections</p> <p><b>Children:</b> variation in FEV<sub>1</sub> of &gt;12% in FEV<sub>1</sub> or &gt;15% in PEF<sup>§</sup> between visits (may include respiratory infections)</p>

Source: Box 1-2 in Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021 [cited September 2021]. 2021. Available from: [www.ginasthma.org](http://www.ginasthma.org).

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BD: bronchodilator (SABA or rapid-acting LABA such as ICS-formoterol); FEV<sub>1</sub>: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta<sub>2</sub>-agonist.

\* If possible, confirm the diagnosis before starting controller treatment.

† BD responsiveness may be lost after starting ICS treatment, during severe exacerbations or viral respiratory infections, or if airflow limitation has become persistent over time. If responsiveness is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. For patients already on controller treatment, see GINA 2021, Box 1-3.

‡ Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over one week.

§ Use the same peak flow meter each time, as PEF may vary by up to 20% between different meters.

**Table E2. Summary of medications and dosages for asthma treatment regimens containing anti-inflammatory reliever**

	Anti-inflammatory reliever (AIR) therapy alone GINA Steps 1–2	Maintenance and reliever therapy (MART) GINA Steps 3, 4 and 5	
Definition	Combination ICS-formoterol taken as needed for symptom relief, without maintenance therapy <i>or, if not available, low-dose ICS taken whenever SABA is taken for symptom relief</i>	Daily maintenance ICS-formoterol PLUS Low-dose ICS-formoterol taken as needed for symptom relief†	
Indications	<b>Mild asthma: GINA Steps 1–2</b>	<b>Moderate-to-severe asthma: GINA Steps 3, 4 and 5</b>	
Explanation	Whenever symptom relief is needed, the patient takes an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA), without daily maintenance treatment <i>or, if ICS-formoterol is not available, they take a low dose of ICS whenever SABA is taken</i>	The patient takes <b>regular daily maintenance</b> controller treatment with low-dose (Step 3) or medium dose (Step 4) combination ICS-formoterol <b>PLUS</b> whenever needed for symptom relief, the patient uses an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA)	
<b>MEDICATIONS AND SUGGESTED DOSAGES BY AGE-GROUP</b>			
	<b>Anti-inflammatory reliever therapy AIR alone: GINA Steps 1–2</b>	<b>MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3</b>	<b>MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEPS 4–5</b>
<b>Budesonide-formoterol</b>			
Adults and adolescents ≥12 years	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose), 1 inhalation as needed for symptom relief.	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]: 2 inhalations twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief
	If symptom persist after a few minutes, another inhalation of ICS-formoterol can be taken. No more than 6 inhalations should be taken on a single occasion. A maximum total of 12 doses (reliever doses plus maintenance doses, if used) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.		
Children 4–11 years	<i>[ICS-formoterol not studied]</i>	Budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation once daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	Suggested dose: budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.
	If symptom persist after a few minutes, another inhalation can be taken. For children, no more than 4 inhalations should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.		
<b>Beclometasone dipropionate-formoterol (BDP-formoterol)</b>			
Beclometasone-formoterol – adults ≥18 years (not studied in children or adolescents)	<i>[BDP-formoterol not studied]</i>	BDP-formoterol 100/6 mcg [87.5/5 mcg delivered dose]: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.  If symptoms persist, another inhalation can be taken. No more than 6 doses should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.	<i>[BDP-formoterol not studied]</i>
<b>Beclometasone dipropionate-albuterol (BDP+SABA)</b>			
Adults ≥18 years, adolescents 12–17 years and children 6–11 years	Beclometasone 50 mcg and albuterol 100 mcg [40 mcg and 90 mcg delivered dose, respectively] 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone (12 puffs).	<i>[ICS-SABA not studied]</i>	<i>[ICS-SABA not studied]</i>

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; ICS: inhaled corticosteroid; MART: maintenance and reliever therapy with ICS-formoterol (also called SMART); SABA: short-acting beta<sub>2</sub>-agonist

ICS-formoterol contains an inhaled corticosteroid (e.g., budesonide or beclometasone) and formoterol, a rapid-onset long-acting beta<sub>2</sub>-agonist.

- **Budesonide-formoterol** is approved for adults and adolescents ≥12 years in many countries for use in as-needed-only ICS-formoterol therapy and MART, and in some countries for MART in children 4–11 years. For budesonide-formoterol, the maximum total number of inhalations that can be taken temporarily in any single day (reliever plus maintenance inhalations, if used) is based on the total dose of formoterol in any day. (72 mcg of formoterol [54 mcg delivered dose] for adults and adolescents, 48 mcg [36 mcg delivered dose] for children 4–11 years)

Most of the studies with budesonide-formoterol as reliever used a dry powder inhaler, but budesonide-formoterol pressurized metered dose inhaler 200/6 mcg [160/4.5 delivered dose] was used in one Step 4 MART study, also with 1 inhalation per as-needed dose (E1).

- **Beclometasone-formoterol** is approved for MART in adults 18 years and older in many countries. A maximum total of 8 inhalations (total of reliever inhalations and maintenance inhalations) can be taken temporarily in a single day.

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- **Other ICS-formoterol formulations** (e.g., mometasone-formoterol, fluticasone-formoterol) have not been studied with either as-needed-only anti-inflammatory reliever (AIR) therapy or MART, but may be able to be substituted if budesonide-formoterol or beclometasone-formoterol are not available. Some ICS-formoterol devices are currently approved only for adults 18 years and older.

Before prescribing any inhaler, ensure that the patient can use it correctly.

The above recommended maximum doses refer to the maximum total dose that can be taken temporarily on any single day. If a patient needs to take more, they should seek medical care the same day. In clinical trials of as-needed-only anti-inflammatory reliever therapy in mild asthma, average use of as-needed low dose budesonide-formoterol was 3–4 inhalations per week, and <0.1% of patients took >8 inhalations of budesonide-formoterol on more than 1 day during the 12-month studies (E2, E3).

For all patients prescribed as-needed only Anti-Inflammatory Reliever (AIR) therapy alone or Maintenance And Reliever Therapy (MART), the *average* frequency of as-needed use of ICS-formoterol in the previous 4 weeks should be reviewed at each visit as part of the assessment of their treatment needs.

Combinations of ICS with non-formoterol long-acting beta<sub>2</sub>-agonists (LABA), or combinations of ICS, LABA and long-acting muscarinic antagonists (LAMA), should not be used as-needed. These medications are recommended only for maintenance treatment. For patients prescribed ICS-LABA-LAMA with a non-formoterol LABA, the reliever should be SABA.

See [downloadable resource: GINA 2021 Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever](#).

## References

- E1. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R, The SMART Study Group. Efficacy and safety of maintenance and reliever combination budesonide–formoterol in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32-42.
- E2. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865-1876.
- E3. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Siwek-Posluszna A, FitzGerald JM. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877-1887.

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Click here for downloadable resource: [GINA 2021 Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever](#)

Accepted Article



## **GINA 2021**

### **Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever**



# GINA 2021 - asthma treatment regimens containing an anti-inflammatory reliever



Accepted Article

## Adults & adolescents 12+ years

**Personalized asthma management**  
Assess, Adjust, Review  
for individual patient needs

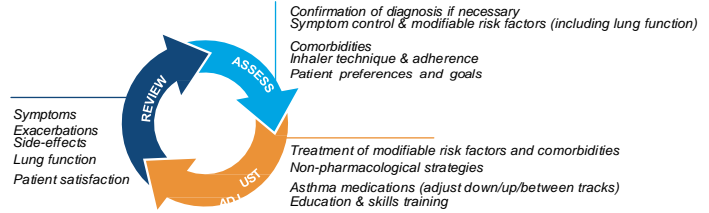
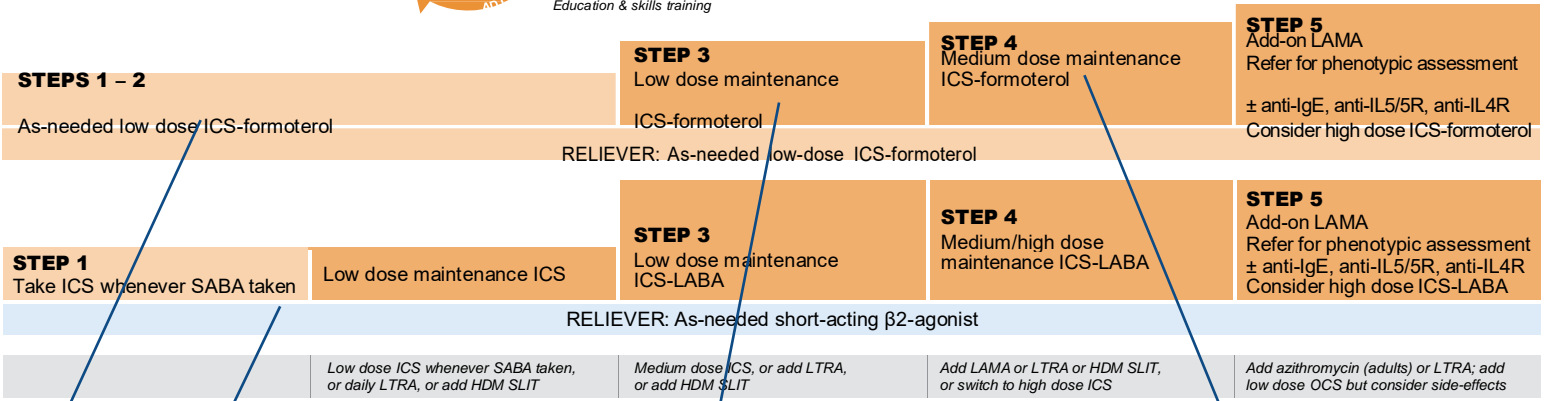


Figure source: Box 3-5A in GINA 2021 Strategy Report

### CONTROLLER and PREFERRED RELIEVER

(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever



### CONTROLLER and ALTERNATIVE RELIEVER

(Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

Other controller options for either track

## MEDICATIONS AND SUGGESTED DOSAGES\* – ADULTS AND ADOLESCENTS ≥12 YEARS

ANTI-INFLAMMATORY RELIEVER (AIR) THERAPY ALONE: GINA STEPS 1–2	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEPS 4–5
<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg, 1 inhalation as needed for symptom relief.	<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg: 2 inhalations twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief
<i>[Beclometasone dipropionate (BDP)-formoterol not studied]</i>	<b>BDP-FORMOTEROL</b> 100/6 mcg: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief. Studied only in adults.	<i>[BDP-formoterol not studied]</i>
<i>If symptom persist after a few minutes, another inhalation of ICS-formoterol can be taken. No more than 6 inhalations should be taken on a single occasion. A maximum total of 12 doses (reliever doses plus maintenance doses, if used) can be taken temporarily in a single day (8 inhalations for BDP-formoterol); if more is needed, medical attention should be sought the same day.</i>		
<b>BECLOMETASONE DIPROPIONATE</b> 50mcg <b>AND ALBUTEROL</b> 100 mcg: 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone (12 puffs).	<i>[ICS-SABA not studied]</i>	

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 AIR: Anti-Inflammatory Reliever; BDP: beclometasone-dipropionate; ICS: inhaled corticosteroid; MART: Maintenance And Reliever Therapy with ICS-formoterol; SABA: short-acting beta<sub>2</sub>-agonist.  
 \*Doses are metered doses. See page 4 for corresponding delivered doses and for more details about medications and dosing. Copyright © 2021. All Rights Reserved. Global Initiative for Asthma – GINA  
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# GINA 2021 - asthma treatment regimens containing an anti-inflammatory reliever

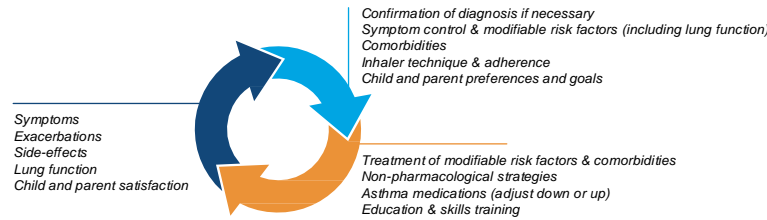
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## Children 6-11 years

Figure source: Box 3-5B in GINA 2021 Strategy Report

**Personalized asthma management:**  
Assess, Adjust, Review

**Asthma medication options:**  
Adjust treatment up and down for individual child's needs



**PREFERRED CONTROLLER**  
to prevent exacerbations and control symptoms

Other controller options

**RELIEVER**

	<b>STEP 1</b>	<b>STEP 2</b>	<b>STEP 3</b>	<b>STEP 4</b>	<b>STEP 5</b>
<b>STEP 1</b>	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE
<b>Other controller options</b>	Consider daily low dose ICS	Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken	Low dose ICS + LTRA	Add tiotropium or add LTRA	Add-on anti-IL5, or add-on low dose ICS, but consider side-effects
<b>RELIEVER</b>	As-needed short-acting beta2-agonist (or ICS-formoterol reliever for MART as above)				

## MEDICATIONS AND SUGGESTED DOSAGES\* – CHILDREN 4 –11 YEARS

ANTI-INFLAMMATORY RELIEVER (AIR) THERAPY ALONE: GINA STEPS 1–2	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 4
[As-needed-only ICS-formoterol not studied in children]	<b>BUDESONIDE-FORMOTEROL</b> 100/6 mcg: 1 inhalation once daily as maintenance treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	Suggested dose: <b>BUDESONIDE-FORMOTEROL</b> 100/6 mcg: 1 inhalation twice daily as maintenance treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.
<b>BECLOMETASONE DIPROPIONATE</b> 50 mcg <b>AND</b> <b>ALBUTEROL</b> 100 mcg: 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone.	If symptom persist after a few minutes, another inhalation can be taken. For children, no more than 4 inhalations should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.	
	[ICS-SABA not studied]	



#### METERED DOSES AND DELIVERED DOSES FOR MEDICATIONS LISTED IN THIS RESOURCE

MEDICATION	METERED DOSE	DELIVERED DOSE
<b>Combination inhalers</b>		
Budesonide-formoterol	200/6 mcg	160/4.5 mcg
	100/6 mcg	80/4.5 mcg
Beclometasone-formoterol	100/6 mcg	87.5/5 mcg
<b>Separate inhalers</b>		
Beclometasone dipropionate	50 mcg	40 mcg
Albuterol (salbutamol)	100 mcg	90 mcg

**Budesonide formoterol** is approved for adults and adolescents 12 years and older in many countries for use in AIR and MART, and in some countries for MART in children 4-11 years. For budesonide-formoterol, the maximum total number of inhalations that can be taken temporarily in any single day (reliever plus maintenance inhalations, if used) is based on the total dose of formoterol in any day (72mcg of formoterol [54 mcg delivered dose] for adults and adolescents, 38 mcg [36 mcg delivered dose] for children 4-11 years). Most of the studies with budesonide-formoterol as reliever used a dry powder inhaler, but budesonide-formoterol pressurized metered dose inhaler 200/6 mcg [160/4.5 delivered dose] was used in one Step 4 MART study, also with 1 inhalation per as-needed dose [Patel et al, Lancet Respir Med 2013; 1: 32-42].

- **Beclometasone-formoterol** is approved for MART in adults 18 years and older in many countries. A maximum total of 8 inhalations (total of reliever inhalations and maintenance inhalations) can be taken temporarily in a single day.
- **Other ICS-formoterol formulations** (e.g. mometasone-formoterol, fluticasone-formoterol) have not been studied with either AIR or MART, but may be able to be substituted if budesonide-formoterol or beclometasone-formoterol are not available. Some ICS-formoterol devices are currently approved only for adults 18+ years.

Before prescribing any inhaler, ensure that the patient can use it correctly.

The above recommended maximum doses refer to the maximum total dose that can be taken on any single day. In clinical trials in mild asthma, average use of as-needed low dose budesonide-formoterol was 3-4 inhalations per week, and <0.1% of patients took >8 inhalations of budesonide-formoterol on more than 1 day during the 12-month studies.

For all patients prescribed Anti-Inflammatory Reliever (AIR) therapy alone or Maintenance And Reliever Therapy (MART), *average* frequency of as-needed use of ICS-formoterol should be reviewed at each visit as part of the assessment of their treatment needs.

ICS-LABA combinations and ICS-LABA-LAMA combinations that contain a non-formoterol LABA should not be used as-needed. These medications are recommended only for maintenance treatment.

The tables displayed are intended to summarize medication classes and dosages that have been studied with AIR and MART therapy (by GINA step). It is not an exhaustive list of all possible medications, and readers are asked to investigate locally available medications as well as local regulatory constraints. Medication names and formulations vary greatly country to country, and this table is intended to serve as framework for clinical decision support rather than exact, specific prescribing guidance.