GINA 2021 Executive summary. Online supplement

Supplementary information

Global Initiative for Asthma (GINA) Strategy 2021 – Executive Summary and Rationale for Key Changes

Authors

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Symptoms/features that support the diagnosis of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze, shortness of breath, chest tightness and cough (descriptors may vary between cultures and by age group)</td>
<td>More than one type of respiratory symptom. In adults, isolated cough is seldom due to asthma. Symptoms occur variably over time and vary in intensity. Symptoms often worse at night or on waking. Symptoms often triggered by exercise, laughter, allergens, cold air. Symptoms often appear or worsen with viral respiratory infections.</td>
</tr>
</tbody>
</table>

2. Confirmed variable expiratory airflow limitation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Considerations, definitions, criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Documented* expiratory airflow limitation</td>
<td>At a time when FEV₁ is reduced, confirm that FEV₁/FVC is reduced compared with the lower limit of normal (usually &gt;0.75–0.80 in adults, &gt;0.90 in children).</td>
</tr>
</tbody>
</table>

AND

2.2 Documented* excessive variability in lung function (one or more of the following):

<table>
<thead>
<tr>
<th>Positive bronchodilator (BD) responsiveness test (reversibility)¹</th>
<th>Adults: increase in FEV₁ &gt;12% and &gt;200 ml (greater confidence if increase &gt;15% and &gt;400 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children: increase in FEV₁ &gt;12% predicted</td>
</tr>
<tr>
<td>Excessive variability in twice-daily PEF³ over 2 weeks</td>
<td>Adults: average daily diurnal PEF variability &gt;10%⁴</td>
</tr>
<tr>
<td>Significant increase in lung function after 4 weeks of anti-inflammatory treatment</td>
<td>Children: average daily diurnal PEF variability &gt;13%⁴</td>
</tr>
</tbody>
</table>

Positive exercise challenge test |

<table>
<thead>
<tr>
<th>Adults: fall in FEV₁ of &gt;10% and &gt;200 ml from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children: fall in FEV₁ of &gt;12% predicted, or PEF &gt;15%</td>
</tr>
</tbody>
</table>

Positive bronchial challenge test (usually only for adults)

<table>
<thead>
<tr>
<th>Adults: variation in FEV₁ of &gt;12% and &gt;200 ml between visits, outside of respiratory infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children: variation in FEV₁ of &gt;12% in FEV₁ or &gt;15% in PEF³ between visits (may include respiratory infections)</td>
</tr>
</tbody>
</table>

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BD: bronchodilator (SABA or rapid-acting LABA such as ICS-formoterol); FEV₁: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta₂-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta₂-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**

<table>
<thead>
<tr>
<th>Anti-inflammatory reliever (AIR) therapy alone GINA Steps 1–2</th>
<th>Maintenance and reliever therapy (MART) GINA Steps 3, 4 and 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td><strong>Daily maintenance ICS-formoterol</strong>&lt;sup&gt;a&lt;/sup&gt; <strong>PLUS</strong> <strong>Low-dose ICS-formoterol taken as needed for symptom relief</strong></td>
</tr>
<tr>
<td>Mild asthma: GINA Steps 1–2</td>
<td>Moderate-to-severe asthma: GINA Steps 3, 4 and 5</td>
</tr>
<tr>
<td><strong>Explanation</strong></td>
<td>The patient takes regular daily maintenance controller treatment with low-dose (Step 3) or medium dose (Step 4) combination ICS-formoterol <strong>PLUS</strong> 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)</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>or, if ICS-formoterol is not available, they take a low dose of ICS whenever SABA is taken</td>
<td></td>
</tr>
</tbody>
</table>

**Budesonide-formoterol**

| 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 maintenance treatment, **PLUS** 1 inhalation as needed for symptom relief. | Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]: 2 inhalations twice daily as maintenance treatment, **PLUS** 1 inhalation as needed for symptom relief. |
| Children 4–11 years | [ICS-formoterol not studied] | Budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation once daily as maintenance treatment, **PLUS** 1 inhalation as needed for symptom relief. | Suggested dose: budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation twice daily as maintenance treatment, **PLUS** 1 inhalation as needed for symptom relief. |

**Beclometasone dipropionate-formoterol (BDP-formoterol)**

| Beclometasone-formoterol – adults ≥18 years (not studied in children or adolescents) | [BDP-formoterol not studied] | BDP-formoterol 100/6 mcg [87.5/5 mcg delivered dose]: 1 inhalation twice daily (or once daily) as maintenance treatment, **PLUS** 1 inhalation as needed for symptom relief. | [BDP-formoterol not studied] |

**Beclometasone dipropionate-albuterol (BDP+SABA)**

| 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). | [ICS-SABA not studied] | [ICS-SABA not studied] |

- 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-agonist
- ICS-formoterol contains an inhaled corticosteroid (e.g., budesonide or beclometasone) and formoterol, a rapid-onset long-acting beta-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 beta2-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**


GINA 2021

Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever
Global Initiative for Asthma (GINA)

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

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

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

**ANTI-INFLAMMATORY RELIEVER (AIR) THERAPY ALONE: GINA STEPS 1–2**

- **BUDESONIDE-FORMOTEROL 200/6 mcg, 1 inhalation as needed for symptom relief.**
  - [Beclometasone dipropionate (BDP)-formoterol not studied]

**MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3**

- **BUDESONIDE-FORMOTEROL 200/6 mcg: 1 inhalation twice daily (or once daily) as maintenance treatment, PLUS 1 inhalation as needed for symptom relief.**
- **BDP-FORMOTEROL 100/6 mcg: 1 inhalation twice daily (or once daily) as maintenance treatment, PLUS 1 inhalation as needed for symptom relief.**

- **BECLOMETASONE DIPROPIONATE 50 mcg AND ALBUTEROL 100 mcg: 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief.**
  - [ICS-SABA not studied]

**STEP 3 – Low dose maintenance ICS-formoterol**

**STEP 4 – Medium dose maintenance ICS-formoterol**

**STEP 5 – High dose maintenance ICS-LABA**

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.

**[ICS-SABA not studied]**

**[BDP-formoterol not studied]**

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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

STEP 1
Low dose ICS taken whenever SABA taken

Consider daily low dose ICS

STEP 2
Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)

Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken

Low dose ICS + LTRA

STEP 3
Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever (MART)

Add tiotropium or add LTRA

Add-on anti-IL5, or add-on low dose OCS, but consider side-effects

STEP 4
Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE

STEP 5
Refer for expert advice

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

BUDESONIDE-FORMOTEROL 100/6 mcg: 1 inhalation once daily as maintenance treatment, PLUS 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.

BUDESONIDE-FORMOTEROL 100/6 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.

[ICS-SABA not studied]

MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3

Suggested dose: BUDESONIDE-FORMOTEROL 100/6 mcg: 1 inhalation twice daily as maintenance treatment, PLUS 1 inhalation as needed for symptom relief.

MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 4

[As-needed-only ICS-formoterol not studied in children]

BECLOMETASONE DIPROPIONATE 50 mcg AND ALBUTEROL 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.


*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
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, 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 (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.

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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.