

Global Initiative for Asthma (GINA)

What's new in GINA 2021?



GINA Global Strategy for Asthma Management and Prevention

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The Global Initiative for Asthma (GINA)



- GINA was established by the WHO and NHLBI in 1993
 - To increase awareness about asthma
 - To improve asthma prevention and management through a coordinated worldwide effort
 - GINA is independent, funded only by the sale and licensing of its reports and figures
- The GINA report is a global evidence-based strategy that can be adapted for local health systems and medicine availability
 - ~500,000 copies of GINA reports downloaded each year from 100 countries
 - Practical focus: multiple flow-charts and tables
- The GINA strategy report is updated every year
 - Twice-yearly cumulative review of new evidence across the whole asthma strategy
- For GINA methodology, see www.ginasthma.com/aboutus/methodology

About GINA recommendations



- Recommendations are framed, not as answers to isolated PICOT questions, but as part of an integrated asthma strategy for symptom control and risk reduction
- Evidence that is considered:
 - RCTs, observational studies, meta-analyses, GRADE reviews if/when available, qualitative studies
 - Critical attention is paid to clinical relevance of study design and generalizability of population
 - For new therapies, usually require at least 2 high quality RCTs plus approval by a major regulator (because of safety data available to regulators)
- Other considerations in making recommendations
 - Patient priorities and preferences
 - Patient behavior, including adherence
 - Current understanding of underlying disease processes
 - Feasibility for implementation in clinical practice
 - Global variation in populations, health systems and medication access

GINA guidance about COVID-19 and asthma

Updated 26 April 2021



GINA Global Strategy for Asthma
Management and Prevention

www.ginasthma.org

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COVID-19 and asthma



- Are people with asthma at increased risk of COVID-19, or severe COVID-19?
 - People with asthma do not appear to be at increased risk of acquiring COVID-19, and systematic reviews have not shown an increased risk of severe COVID-19 in people with well-controlled, mild-to-moderate asthma
- Are people with asthma at increased risk of COVID-19-related death?
 - Overall, people with well-controlled asthma are not at increased risk of COVID-19-related death (*Williamson, Nature 2020; Liu et al JACI IP 2021*)
 - However, the risk of COVID-19 death was increased in people who had recently needed oral corticosteroids (OCS) for their asthma (*Williamson, Nature 2020*) and in hospitalized patients with severe asthma (*Bloom, Lancet Respir Med 2021*).
- What are the implications for asthma management?
 - It is important to continue good asthma management (as described in the GINA report), with strategies to maintain good symptom control, reduce the risk of severe exacerbations and minimise the need for OCS
- Have there been more asthma exacerbations during the pandemic?
 - No. In 2020, many countries saw a *reduction* in asthma exacerbations and influenza-related illness. The reasons are not precisely known, but may be due to handwashing, masks and social/physical distancing that reduced the incidence of other respiratory infections, including influenza

COVID-19 and asthma - medications



- Advise patients to continue taking their prescribed asthma medications, particularly inhaled corticosteroids (ICS)
 - For patients with severe asthma, continue biologic therapy or oral corticosteroids if prescribed
- Are ICS protective in COVID-19?
 - In one study of hospitalized patients aged ≥ 50 years with COVID-19, ICS use in those with asthma was associated with lower mortality than in patients without an underlying respiratory condition (*Bloom, Lancet RM 2021*)
- Make sure that all patients have a written asthma action plan, advising them to:
 - Increase controller and reliever medication when asthma worsens (see GINA report Box 4-2)
 - Take a short course of OCS when appropriate for severe asthma exacerbations
- Avoid nebulizers where possible, to reduce the risk of spreading virus
 - Pressurized metered dose inhaler via a spacer is preferred except for life-threatening exacerbations
 - Add a mouthpiece or mask to the spacer if required

COVID-19 and asthma – infection control



- Avoid spirometry in patients with confirmed or suspected COVID-19, or if community transmission of COVID-19 is occurring in your region
 - Follow aerosol, droplet and contact precautions if spirometry is needed
 - Consider asking patients to monitor PEF at home, if information about lung function is needed
- Follow strict infection control procedures if aerosol-generating procedures are needed
 - Nebulization, oxygen therapy (including nasal prongs), sputum induction, manual ventilation, non-invasive ventilation and intubation
- Follow local health advice about hygiene strategies and use of personal protective equipment, as new information becomes available in your country or region

COVID-19 vaccines and asthma



- Have COVID-19 vaccines been studied in people with asthma?
 - Yes. Many types of COVID-19 vaccines have been studied and are being used worldwide
 - New evidence, including in people with asthma, will emerge over time
- Are COVID-19 vaccines safe in people with allergies?
 - In general, allergic reactions to vaccines are rare
 - The Pfizer/BioNTech and Moderna COVID-19 vaccines should be administered in a healthcare setting where anaphylaxis can be treated if it occurs
 - These vaccines should not be administered to patients with a history of severe allergic reaction to polyethylene glycol, or any other vaccine ingredient. More details from ACIP are [here](#)
 - As always, patients should speak to their healthcare provider if they have concerns
- Usual vaccine precautions apply, for example:
 - Ask if the patient has a history of allergy to any components of the vaccine
 - If the patient has a fever or another infection, delay vaccination until they are well
- At present, based on the risks and benefits, and with the above caution, GINA recommends COVID-19 vaccination for people with asthma

COVID-19 vaccines and asthma



- COVID-19 vaccination and biologic therapy
 - We suggest that biologic therapy and COVID-19 vaccine should not be given on the same day, so that adverse effects of either can be more easily distinguished
- After COVID-19 vaccination
 - Current advice from the United States Centers for Disease Control and Prevention (CDC) is that people who have been fully vaccinated against COVID-19 should continue to wear a mask in crowded settings. Further details are [here](#)
- Influenza vaccination
 - Remind people with asthma to have an annual influenza vaccination
 - A gap of 14 days between COVID-19 vaccination and influenza vaccination is recommended by [CDC](#)

- GINA will update advice about COVID-19 and asthma as new data become available

GINA 2021: Treatment of asthma in adults and adolescents



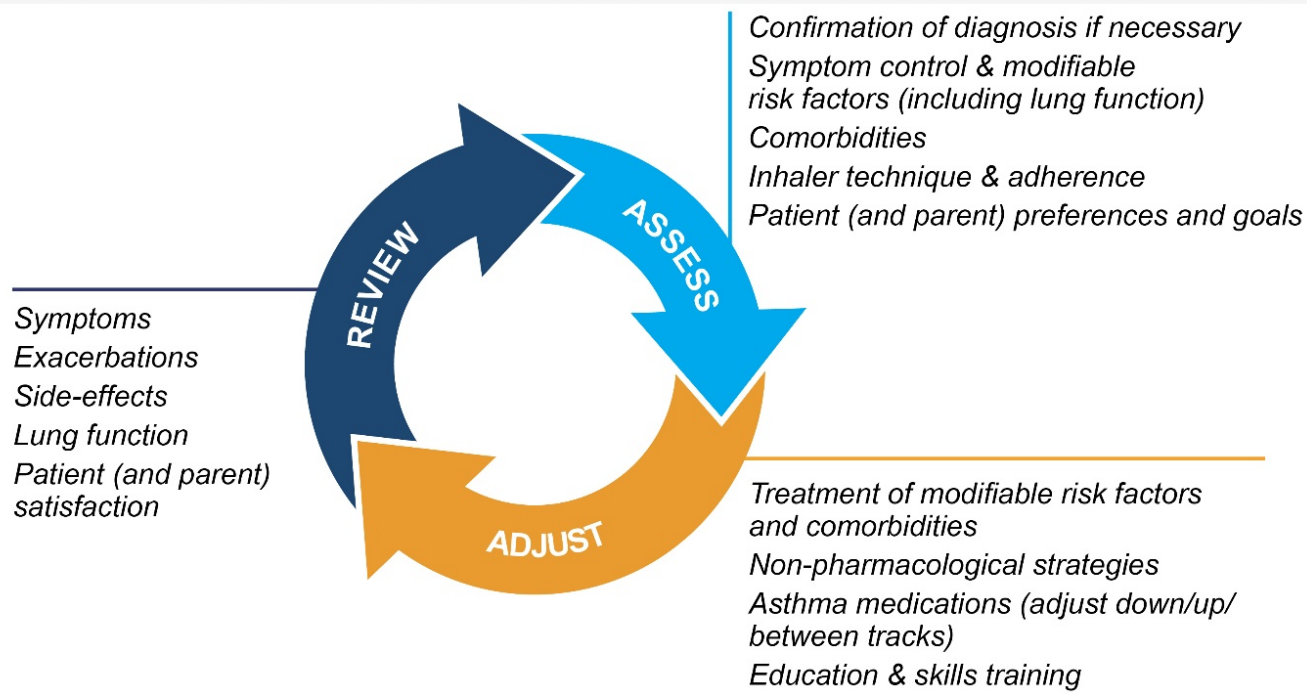
GINA Global Strategy for Asthma Management and Prevention

About asthma



- Asthma is the most common chronic non-communicable disease, affecting over 260 million people globally in 2019
- Asthma is characterized by **variable respiratory symptoms** such as wheeze, shortness of breath, chest tightness and cough, and **variable expiratory airflow limitation**. It is usually associated with **airway inflammation**
- People with asthma often have periods of worsening symptoms and worsening airway obstruction, called **exacerbations** (also called attacks or flare-ups), that can be fatal
- Most of the morbidity and mortality associated with asthma is preventable, particularly with use of inhaled corticosteroids

Personalized asthma management



- NOT just about medications, NOT one-size-fits-all





A reminder – a key change in asthma management



EDITORIAL
GINA 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel ¹, J. Mark FitzGerald², Eric D. Bateman³, Leonard B. Bacharier⁴, Allan Becker⁵, Guy Brusselle⁶, Roland Buhl⁷, Alvaro A. Cruz⁸, Louise Fleming ⁹, Hiromasa Inoue¹⁰, Fanny Wai-san Ko ¹¹, Jerry A. Krishnan¹², Mark L. Levy ¹³, Jiangtao Lin¹⁴, Søren E. Pedersen¹⁵, Aziz Sheikh¹⁶, Arzu Yorgancioglu¹⁷ and Louis-Philippe Boulet¹⁸

GINA 2019 – landmark changes in asthma management



- For safety, GINA no longer recommends SABA-only treatment for Step 1 in adults and adolescents
 - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
- GINA now recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations
 - The ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low dose ICS-formoterol
- This is a population-level risk reduction strategy
 - Other examples: statins, anti-hypertensives
 - The aim is to reduce the probability of serious adverse outcomes at a population level
 - Individual patients may not necessarily experience (or be aware of) short-term clinical benefit

ICS: inhaled corticosteroids; SABA: short-acting beta₂-agonist

Background - the risks of 'mild' asthma



- Patients with apparently mild asthma are still at risk of serious adverse events
 - 30–37% of adults with acute asthma
 - 16% of patients with near-fatal asthma
 - 15–20% of adults dying of asthma

} had symptoms less than weekly in previous 3 months (*Dusser, Allergy 2007*)
- Exacerbation triggers are unpredictable (viruses, pollens, pollution, poor adherence)
- Inhaled SABA has been first-line treatment for asthma for 50 years
 - Dating from an era when asthma was thought to be a disease of bronchoconstriction
 - Its role has been reinforced by rapid relief of symptoms and low cost
 - Starting treatment with SABA trains the patient to regard it as their primary asthma treatment

SABA: short-acting beta₂-agonist

Background - the risks of SABA-only treatment



- Regular use of SABA, even for 1–2 weeks, is associated with adverse effects
 - β -receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (*Hancox, Respir Med 2000*); increased allergic response, and increased eosinophilic airway inflammation (*Aldridge, AJRCCM 2000*)
- Higher use of SABA is associated with adverse clinical outcomes
 - Dispensing of ≥ 3 canisters per year (i.e. daily use) is associated with higher risk of severe exacerbations (*Stanford, AAI 2012; Nwaru, ERJ 2021*)
 - Dispensing of ≥ 12 canisters per year is associated with much higher risk of death (*Suissa, AJRCCM 1994; Nwaru, ERJ 2021*)
- Inhaled corticosteroids reduce the risk of asthma deaths, hospitalization and exacerbations requiring oral corticosteroids (OCS) (*Suissa, NEJM 2000 & 2002; Pauwels, Lancet 2003*)
 - BUT adherence is poor, particularly in patients with mild or infrequent symptoms
- A safe and effective alternative was needed for mild asthma

OCS: oral corticosteroids; SABA: short-acting beta₂-agonist

The GINA 2021 treatment figure for adults and adolescents



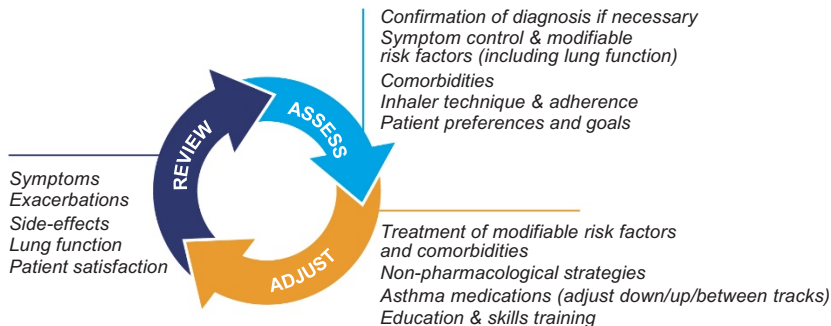
- For clarity, the GINA treatment figure now shows two ‘tracks’, based on evidence about outcomes with the two reliever choices across asthma severity
- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred approach**
 - Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and similar lung function
- **Track 2, with SABA as the reliever, is an alternative approach**
 - Use this if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current controller therapy
 - Before considering a regimen with SABA reliever, consider whether the patient is likely to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- 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

ICS: inhaled corticosteroids; SABA: short-acting beta₂-agonist

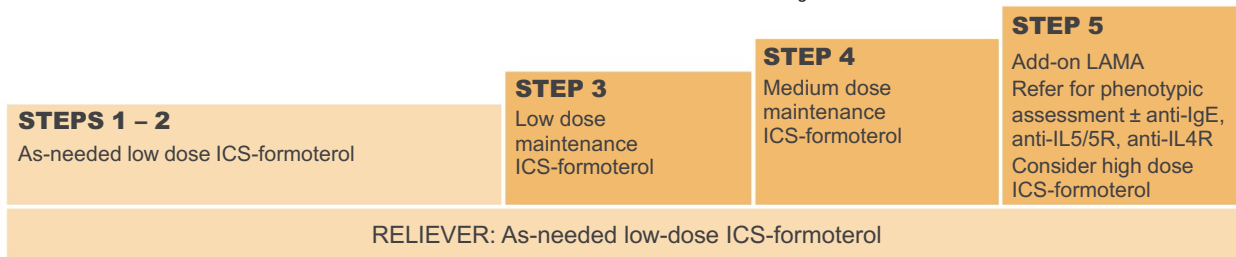
Adults & adolescents 12+ years

Personalized asthma management

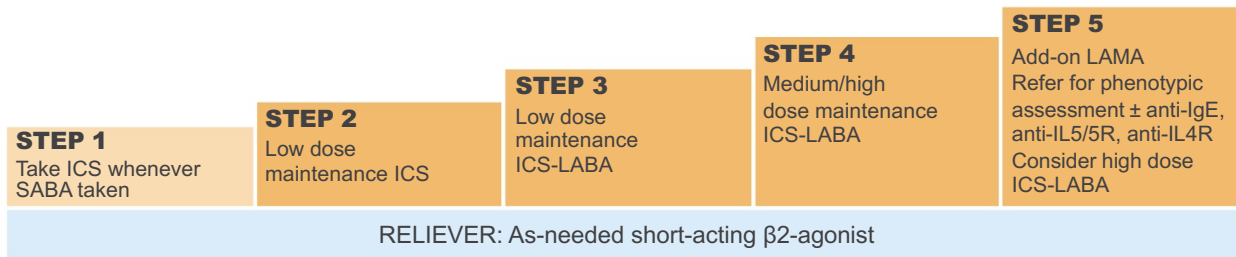
Assess, Adjust, Review
for individual patient needs



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 switch to high dose ICS	Add azithromycin (adults) or LTRA; add low dose OCS but consider side-effects
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GINA Track 1 (preferred): the reliever is low dose ICS-formoterol



- Why is this preferred for adults and adolescents?
 - Because using low dose ICS-formoterol as reliever reduces the risk of severe exacerbations compared with regimens with SABA as reliever, with similar symptom control
- How is it used?
 - When a patient at any treatment step has asthma symptoms, they use low dose ICS-formoterol in a single inhaler for symptom relief
 - In Steps 3–5, patients also take ICS-formoterol as their daily controller treatment. Together, this is called ‘maintenance and reliever therapy’ or ‘MART’
- When should it not be used?
 - ICS-formoterol should not be used as the reliever in patients prescribed a different ICS-LABA for their controller therapy

ICS: inhaled corticosteroids; SABA: short-acting beta₂-agonist

GINA Track 2 (alternative): the reliever is SABA



- When should this be used?
 - This is an alternative approach for adults and adolescents if Track 1 is not possible, or is not preferred by a patient with no exacerbations on their current therapy
- How is it used?
 - In Step 1, the patient takes a SABA and a low dose ICS together for symptom relief when symptoms occur, in a combination inhaler, or with the ICS taken right after the SABA
 - In Steps 2–5, the patient takes ICS-containing controller medication regularly every day, and uses a SABA (alone) for symptom relief
- When should it not be used?
 - Before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their prescribed ICS-containing controller therapy. If they are poorly adherent, they will be at higher risk of exacerbations

ICS: inhaled corticosteroids; SABA: short-acting beta₂-agonist

Evidence for as-needed ICS-formoterol in Step 2 (n=9,565)



- Compared with SABA alone
 - Severe exacerbations reduced by about two-thirds in a large double-blind study (*O'Byrne, NEJMed 2018*) and in an open-label study in patients previously taking SABA alone (*Beasley, NEJMed 2019*)
 - Exercise-induced bronchoconstriction: greater reduction (*Lazarinis, Thorax 2014*)
- Compared with maintenance low dose ICS with as-needed SABA
 - Severe exacerbations: non-inferior in 2 large double-blind studies (*O'Byrne NEJMed 2018; Bateman NEJMed 2018*) and superior in 2 open-label RCTs (*Beasley NEJMed 2019; Hardy Lancet 2019*)
 - ICS dose: approx. 25–50% of dose compared with maintenance low dose ICS
 - Symptom control: very small difference in ACQ-5 (~0.1 vs MCID 0.5), not cumulative over 12 mths
 - Lung function: very small difference (~30–50 mL), not cumulative
 - FeNO: very small difference, not cumulative
 - Exercise-induced bronchoconstriction: no significant difference (*Lazarinis, Thorax 2014*)

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; MCID: minimal clinically important difference; SABA: short-acting beta₂-agonist

Other considerations for as-needed ICS-formoterol in Step 2



- Severe exacerbations can occur in mild asthma and are often unpredictable
 - Viral infections, allergen exposure, air pollution, stress
- ICS are highly effective in mild asthma, but patients are often poorly adherent
- Even occasional short courses of OCS are associated with increased risk
 - Osteoporosis, diabetes, cataract etc (*Price, J Asthma Allergy 2018*)
- Differences in symptom control and lung function were not clinically important
 - Primary outcome variable of one study (*O'Byrne NEJMed 2018*) was 'well-controlled asthma weeks', but this outcome was not considered reliable as it was based on an earlier concept of asthma control, and was systematically biased against the as-needed ICS-formoterol treatment group
- Phenotyping is not needed for treatment with as-needed ICS-formoterol
 - No significant difference in treatment effect compared with as-needed SABA or daily ICS with high vs low baseline eosinophils or FeNO (*Beasley NEJMed 2019; Hardy Lancet 2019*)

FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; OCS: oral corticosteroids; SABA: short-acting beta₂-agonist

Why did GINA extend as-needed ICS-formoterol to Step 1?



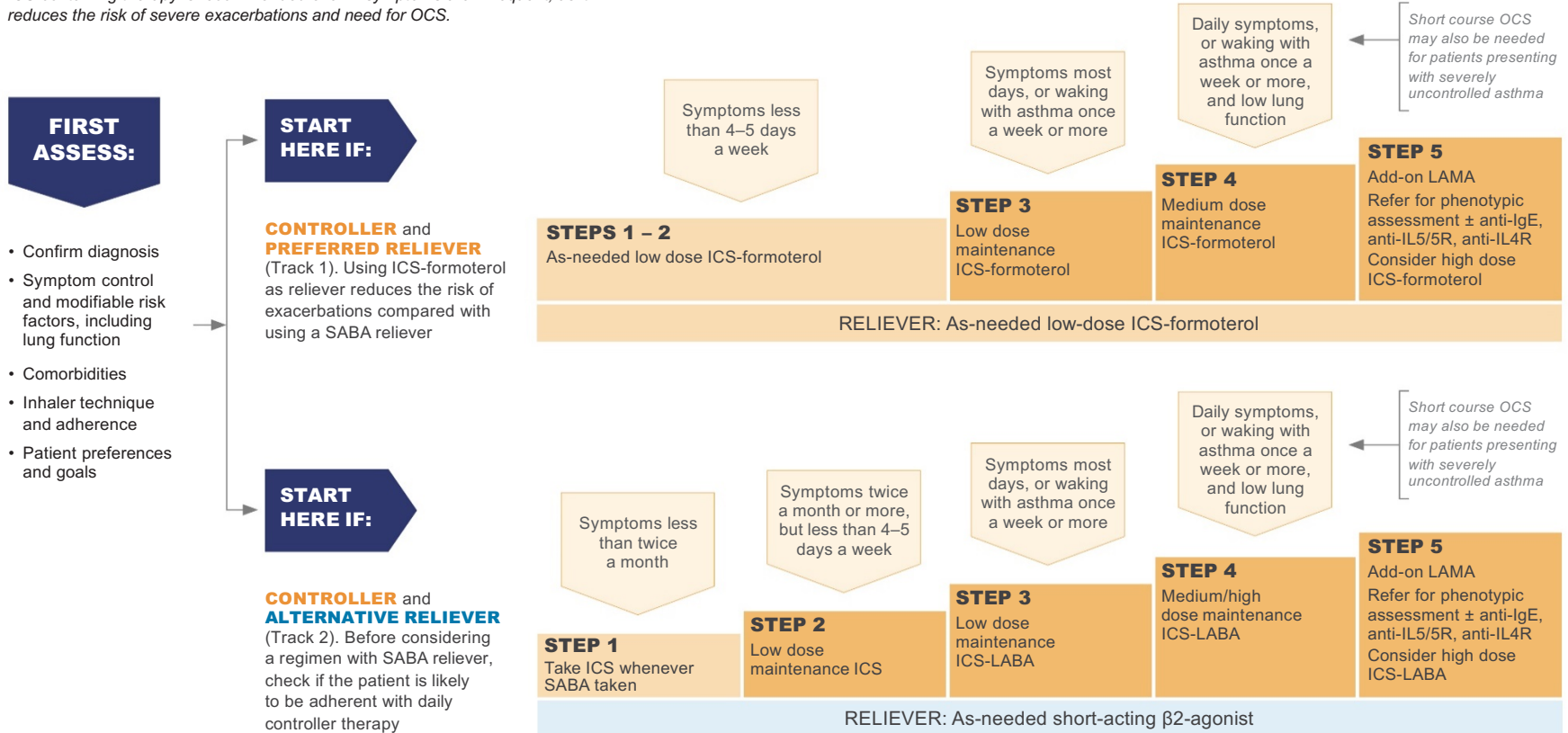
- There is no evidence for safety or efficacy of SABA-only treatment
- Patients with infrequent symptoms can still have severe or fatal exacerbations
 - Often unpredictable: viral infections, allergen exposure, air pollution, stress
 - Even occasional courses of OCS increase the risk of serious adverse outcomes
- There is indirect evidence about safety and efficacy of as-needed ICS-formoterol from four large RCTs in patients eligible for Step 2 treatment by GINA 2012 or 2014 criteria
- The distinction between symptoms $<$ and \geq twice/month (or twice/week e.g. NAEP) is arbitrary, not evidence-based
 - No plausible mechanistic difference
 - No difference in risk reduction with ICS or ICS-formoterol by symptom frequency
 - Even a single day of higher ICS-formoterol use reduces the risk of progression to needing OCS (*O'Byrne, Lancet Respir Med 2021*)
- Starting with SABA alone trains the patient to regard it as their primary asthma treatment
 - Goals of treatment are symptom control AND risk reduction, across asthma severity

ICS: inhaled corticosteroids; OCS: oral corticosteroids; SABA: short-acting beta₂-agonist

STARTING TREATMENT

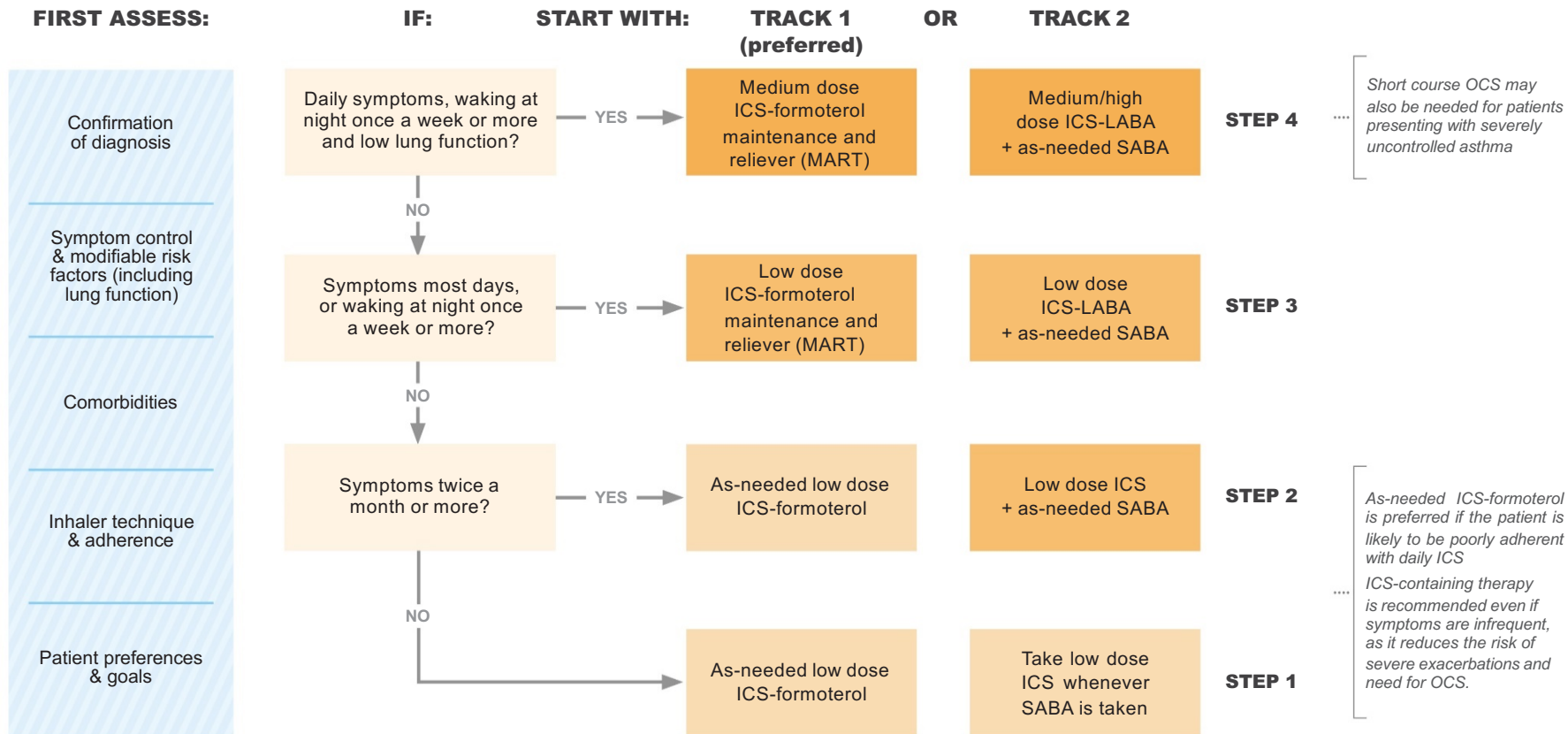
in adults and adolescents with a diagnosis of asthma

Track 1 is preferred if the patient is likely to be poorly adherent with daily controller ICS-containing therapy is recommended even if symptoms are infrequent, as it reduces the risk of severe exacerbations and need for OCS.



STARTING TREATMENT

in adults and adolescents 12+ years with a diagnosis of asthma



Other changes in GINA 2021 – mild asthma



- There are many definitions of mild asthma
 - Current definition: Asthma that is able to be well-controlled with reliever alone or low dose ICS; but severity cannot be assessed until the patient has been on treatment for several months
 - In research studies, mild asthma is often defined by treatment with SABA alone or low dose ICS (but patients may be being under- or over-treated)
 - Patients and clinicians often consider ‘mild asthma’ to mean infrequent or mild symptoms
- GINA does not distinguish between ‘intermittent’ and ‘mild persistent’ asthma
 - Historically, this was an arbitrary distinction, based on an assumption that patients with symptoms twice a week or less would not benefit from ICS
 - Patients with so-called ‘intermittent’ asthma are still at risk of severe exacerbations
- GINA is planning to review the definition of mild asthma during 2021

ICS: inhaled corticosteroids

Maintenance and reliever therapy (MART) in Steps 3–5



- Maintenance and reliever therapy (MART) with ICS-formoterol reliever reduces the risk of severe exacerbations compared with regimens with SABA reliever
 - Compared with same dose or higher dose ICS-LABA, in patients with history of severe exacerbations (*Sobieraj, JAMA 2018*)
 - Compared with conventional best practice, in broad populations (*Cates, Cochrane 2013, Demoly Respir Med 2009*)
- Maintenance and reliever therapy (MART) in Step 4
 - ICS responsiveness varies, and some patients whose asthma is uncontrolled on MART with low dose ICS-formoterol despite good adherence and correct inhaler technique may benefit from increasing the total daily maintenance dose to medium
- Maintenance and reliever therapy (MART) in Step 5
 - There is no direct evidence about initiating MART in patients receiving add-on treatment such as LAMA or biologic therapy, but if a patient is already taking MART, switching them to conventional ICS-LABA plus as-needed SABA may increase the risk of exacerbations

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; OCS: oral corticosteroids; SABA: short-acting beta₂-agonist

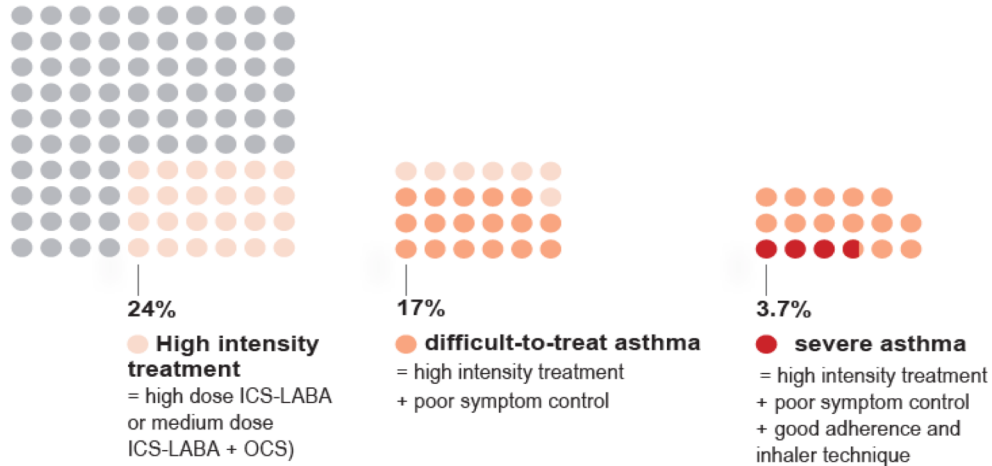
Asthma severity – severe asthma



- To avoid confusion, the definition of severe asthma has been reworded without reference to GINA steps, as these have changed over time
- Severe asthma is asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist

What proportion of adults have severe asthma?



Data from Hekking et al, JACI 2015

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; OCS: oral corticosteroids

Add-on long-acting muscarinic antagonists (LAMA)



- Step 5 recommendations for add-on LAMA have been expanded to include combination ICS-LABA-LAMA, if asthma is persistently uncontrolled despite ICS-LABA
 - Add-on tiotropium in separate inhaler (ages ≥ 6 years)
 - Triple combinations (ages ≥ 18 years): beclometasone-formoterol-glycopyrronium; fluticasone furoate-vilanterol-umeclidinium; mometasone-indacaterol-glycopyrronium
- Lung function:
 - Adding LAMA to medium or high dose ICS-LABA modestly improves lung function (Evidence A) but not symptoms
- Severe exacerbations
 - In some studies, add-on LAMA modestly increased the time to severe exacerbation requiring OCS (Evidence B)
 - For patients with exacerbations, it is important to ensure that the patient receives sufficient ICS, i.e. at least medium dose ICS-LABA, before considering adding a LAMA

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; LAMA: long-acting muscarinic antagonist; OCS: oral corticosteroids

Add-on azithromycin



- Add-on azithromycin three days a week has been confirmed as an option for consideration after specialist referral
 - Significantly reduces exacerbations in patients taking high dose ICS-LABA
 - Significantly reduces exacerbations in patients with eosinophilic or non-eosinophilic asthma
 - No specific evidence published for azithromycin in patients taking medium dose ICS-LABA (*Hiles et al, ERJ 2019*)
- Before considering add-on azithromycin
 - Check sputum for atypical mycobacteria
 - Check ECG for long QTc (and re-check after a month of treatment)
 - Consider the risk of increasing antimicrobial resistance (population or personal)

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist

Add-on biologic therapy for severe Type 2 asthma



- When assessing eligibility, repeat blood eosinophils if low at first assessment
 - One study found that 65% patients on medium or high dose ICS-LABA shifted their eosinophil category during 12 months' follow-up (*Lugogo et al, Ann Allergy Asthma Immunol 2020*)
- Additional indications for these therapies in Europe and/or USA have been listed
 - Omalizumab: chronic idiopathic urticaria, nasal polyposis
 - Mepolizumab: hypereosinophilic syndrome, eosinophilic granulomatosis with polyangiitis (EGPA)
 - Benralizumab: no additional indications at present
 - Dupilumab: chronic rhinosinusitis with nasal polyposis (CRSwNP); atopic dermatitis
- Check local regulatory approvals and eligibility criteria

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist

GINA 2021: Treatment of asthma in children



GINA Global Strategy for Asthma Management and Prevention

GINA 2021 treatment figure for children 6–11 years



- This figure was updated for consistency with the existing recommendations in the text
- Step 1 (children with symptoms less than twice/month)
 - Taking ICS whenever SABA taken is preferred over daily ICS, as poor adherence highly likely
- Step 2
 - Daily ICS is preferred over taking ICS whenever SABA taken, as much stronger evidence for efficacy and safety
- Step 3
 - Maintenance and reliever therapy (MART) with very low dose ICS-formoterol is included in options for children, to reduce risk of severe exacerbations (*Bisgaard et al, Chest 2006*)
 - Other options: low dose ICS-LABA, or medium dose ICS
- Step 4
 - Medium dose ICS-LABA, or low dose ICS-formoterol MART
 - Refer for expert opinion

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; MART: maintenance and reliever therapy; SABA: short-acting beta₂-agonist

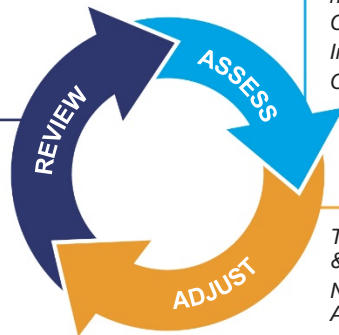
Children 6-11 years



Personalized asthma management:

Assess, Adjust, Review

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:

Adjust treatment up and down for individual child's needs

PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

	STEP 1 Low dose ICS taken whenever SABA taken	STEP 2 Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	STEP 3 Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	STEP 4 Medium dose ICS-LABA, OR low dose [†] ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	STEP 5 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
RELIEVER	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).

STARTING TREATMENT

Children 6–11 years with a diagnosis of asthma



ASSESS:

Confirmation of diagnosis
Symptom control & modifiable risk factors (including lung function)

Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

START HERE IF:

Symptoms less than twice a month

Symptoms twice a month or more, but less than daily

Symptoms most days, or waking with asthma once a week or more

Symptoms most days, or waking with asthma once a week or more, and low lung function

Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

	<p>STEP 1</p> <p>Low dose ICS taken whenever SABA taken</p>	<p>STEP 2</p> <p>Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)</p>	<p>STEP 3</p> <p>Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)</p>	<p>STEP 4</p> <p>Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice</p>	<p>STEP 5</p> <p>Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE</p>
Other controller options	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

RELIEVER

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).

SUGGESTED INITIAL CONTROLLER TREATMENT

in CHILDREN 6-11 years with a diagnosis of asthma



FIRST ASSESS:

- Confirmation of diagnosis

- Symptom control & modifiable risk factors (including lung function)

- Comorbidities

- Inhaler technique & adherence

- Child and parent preferences and goals

IF:

Symptoms most days, waking at night \geq once a week and low lung function?

YES

Medium dose ICS-LABA or low dose MART*. Refer for expert advice

STEP 4

NO

Symptoms most days, or waking at night \geq once a week?

YES

Low dose ICS-LABA or medium dose ICS or very low dose MART*†

STEP 3

NO

Symptoms twice a month or more?

YES

Daily low dose ICS

STEP 2

NO

Take ICS whenever SABA taken

STEP 1

Short course OCS may also be needed for patients presenting with severely uncontrolled asthma

* Low dose: BUD-FORM 200/6 mcg; † Very low dose: BUD-FORM 100/6 mcg (metered doses)
MART= maintenance and reliever therapy (ICS-formoterol as both maintenance and reliever)

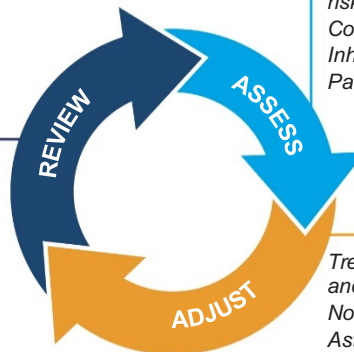
Children 5 years and younger



Personalized asthma management:

Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Parent satisfaction



Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Parent preferences and goals

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

Asthma medication options:

Adjust treatment up and down for individual child's needs

PREFERRED CONTROLLER CHOICE

Other controller options

RELIEVER

CONSIDER THIS STEP FOR CHILDREN WITH:

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS	Continue controller & refer for specialist assessment
Other controller options		Daily leukotriene receptor antagonist (LTRA), or intermittent short courses of ICS at onset of respiratory illness	Low dose ICS + LTRA Consider specialist referral	Add LTRA, or increase ICS frequency, or add intermittent ICS
RELIEVER	As-needed short-acting β_2 -agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥ 3 per year. Give diagnostic trial for 3 months. Consider specialist referral.	Asthma diagnosis, and asthma not well-controlled on low dose ICS	Asthma not well-controlled on double ICS
		Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥ 3 exacerbations per year.	Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	

Other changes in GINA 2021



GINA Global Strategy for Asthma Management and Prevention

Low, medium and high doses of different ICS



- NOT a table of equivalence
 - Suggested total daily doses for 'low', 'medium' and 'high' dose treatment options
 - Based on available studies (very few) and product information
 - Does NOT imply potency equivalence
- Doses may be country-specific depending on local availability, regulatory labelling and clinical guidelines; and for mometasone, depending on whether LAMA added
- Clinical relevance
 - Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma
 - ICS responsiveness varies between patients, so some patients may need medium dose ICS if their asthma is uncontrolled despite good adherence and correct technique
 - High dose ICS (in combination with LABA or separately) is needed by very few patients
 - Its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits

ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; LAMA: long-acting muscarinic antagonist

Low, medium and high ICS doses: adults/adolescents



Adults and adolescents (12 years and older)

Inhaled corticosteroid	Total daily ICS dose (mcg) – see notes above		
	Low	Medium	High
Beclometasone dipropionate (pMDI, standard particle, HFA)	200-500	>500-1000	>1000
Beclometasone dipropionate (DPI or pMDI, extrafine particle, HFA)	100–200	>200–400	>400
Budesonide (DPI, or pMDI, standard particle, HFA)	200–400	>400–800	>800
Ciclesonide (pMDI, extrafine particle, HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100		200
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	100–250	>250–500	>500
Mometasone furoate (DPI)	Depends on DPI device – see product information		
Mometasone furoate (pMDI, standard particle, HFA)	200-400		>400

This is NOT a table of equivalence. These are suggested total daily doses for the ‘low’, ‘medium’ and ‘high’ dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; * see product information

Low, medium and high ICS doses: children 6-11 years



Children 6–11 years – see notes above (for children 5 years and younger, see Box 6-6, p.160)

Beclometasone dipropionate (pMDI, standard particle, HFA)	100–200	>200–400	>400
Beclometasone dipropionate (pMDI, extrafine particle, HFA)	50-100	>100-200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebulas)	250–500	>500–1000	>1000
Ciclesonide (pMDI, extrafine particle*, HFA)	80	>80-160	>160
Fluticasone furoate (DPI)		50	n.a.
Fluticasone propionate (DPI, or pMDI, standard particle, HFA)	50-100	>100-200	>200
Mometasone furoate (pMDI, standard particle, HFA)		100	200

This is NOT a table of equivalence. These are suggested total daily doses for the ‘low’, ‘medium’ and ‘high’ dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; * see product information

Low, medium and high ICS doses: children 5 years and younger



Inhaled corticosteroid	Low total daily dose (mcg) (age-group with adequate safety and effectiveness data)
BDP (pMDI, standard particle, HFA)	100 (ages 5 years and older)
BDP (pMDI, extrafine particle, HFA)	50 (ages 5 years and older)
Budesonide nebulized	500 (ages 1 year and older)
Fluticasone propionate (pMDI, standard particle, HFA)	50 (ages 4 years and older)
Fluticasone furoate (DPI)	Not sufficiently studied in children 5 years and younger)
Mometasone furoate (pMDI, standard particle, HFA)	100 (ages 5 years and older)
Ciclesonide (pMDI, extrafine particle, HFA)	Not sufficiently studied in children 5 years and younger)

This is NOT a table of equivalence. These are suggested total daily doses for the 'low' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; ICS: inhaled corticosteroid; pMDI: pressurized metered dose inhaler; * see product information

Other changes in GINA 2021



- Description of populations in clinical trials or observational studies
 - Describe treatment taken, not Step number; do not impute severity
 - For example, 'patients taking medium dose ICS-LABA' (not 'Step 4 treatment', not 'moderately severe asthma')
- Asthma Control Questionnaire
 - Interpretation of cutpoints has been clarified
 - ACQ-5 is preferred over ACQ-6 or ACQ-7, because of inflexibility of reliever options in Q6, and to avoid stepping up asthma treatment in patients with persistent airflow limitation
- Withholding times for bronchodilators updated to ATS Spirometry guidelines
 - SABA ≥ 4 hours, twice-daily LABA ≥ 24 hours, once-daily LABA ≥ 36 hours
- Primary prevention of asthma
 - 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
- For additional changes, see GINA report 'What's new in GINA 2021?'

LABA: long-acting beta₂-agonist; SABA: short-acting beta₂-agonist

To be addressed in future GINA reports



- The definition of mild asthma
- Assessment of symptom control in patients whose reliever is ICS-formoterol
- Evidence about subcutaneous allergen immunotherapy and sublingual allergen immunotherapy
- Advice about COVID-19 will be updated during the year as new evidence becomes available

GINA methodology – additional details



- The GINA report is a global strategy document
 - Regulatory approvals and submissions differ from country to country
 - Many recommendations are 'off-label' in various countries, particularly for paediatrics
- For new therapies
 - Regulatory agencies often receive more safety data than are in peer-reviewed literature
 - GINA makes recommendations based on the best available evidence, after approval by at least one major regulatory agency (e.g. EMA, FDA)
- For existing medications with evidence for new regimens or populations
 - If satisfied with evidence for safety and effectiveness, GINA may consider making recommendations that are not covered by a regulatory indication in any country at the time
 - Examples: long-term macrolides for moderate-severe asthma (2018); as-needed ICS-formoterol (2019), taking ICS whenever SABA is taken, for mild asthma (2019)
- When assessing and treating patients
 - Use your own professional judgment
 - Take into account local and national guidelines and payer eligibility criteria, and licensed drug doses

Questions?



GINA Global Strategy for Asthma
Management and Prevention