Global Initiative for Asthma (GINA)

What's new in GINA 2022?

GINA Global Strategy for Asthma Management and Prevention

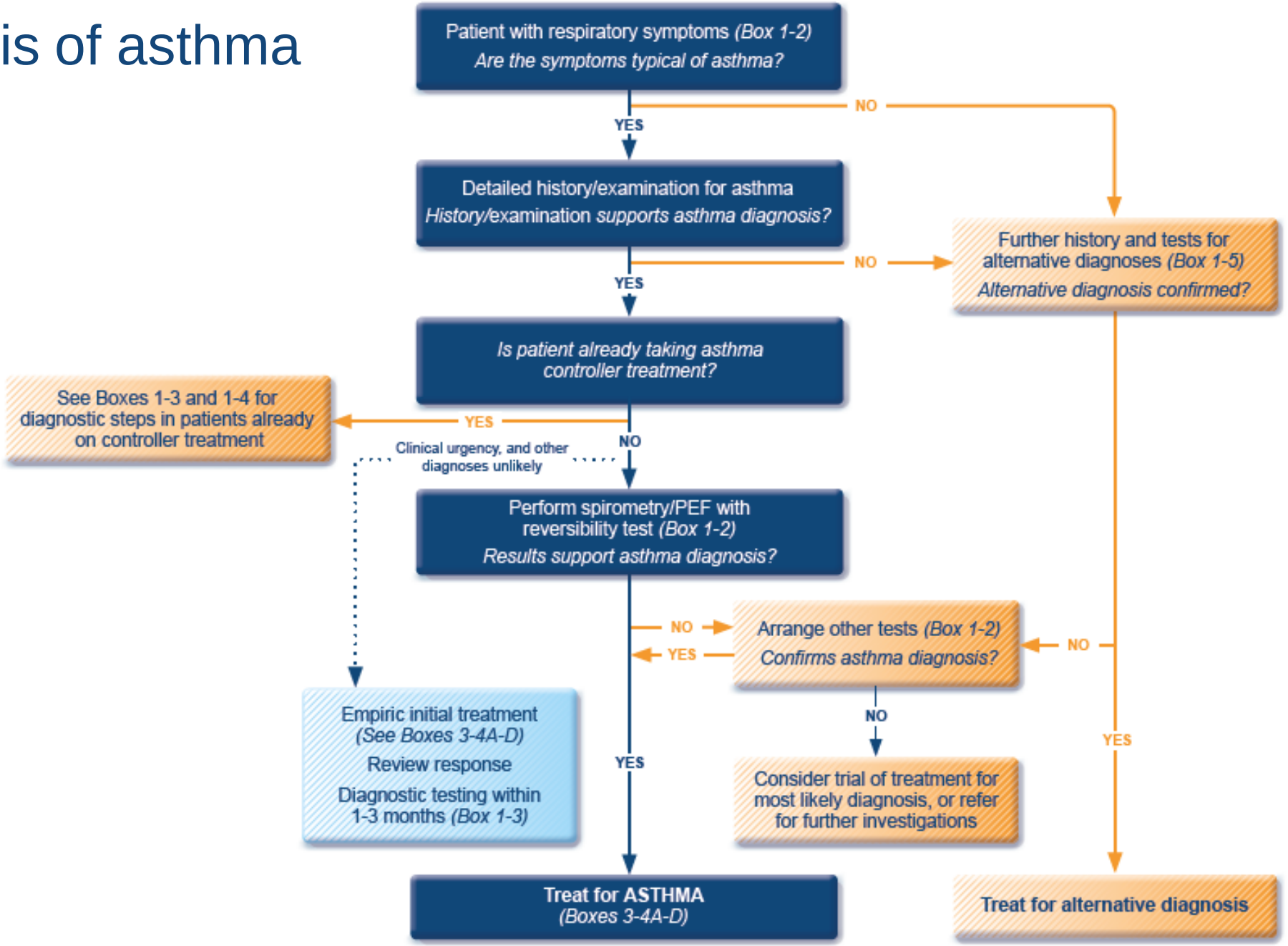
The Global Initiative for Asthma (GINA)

- 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
  - The Science Committee reviews published GRADE reviews, when available
  - Careful attention is paid to clinical relevance of study designs and generalizability of populations
  - Extensive external review before publication
- For detailed description of GINA methodology, see www.ginasthma.com/aboutus/methodology

Diagnosis of asthma

- The diagnosis of asthma is based on a history of variable respiratory symptoms and demonstration of variable expiratory airflow limitation
  - Test before treating, wherever possible
  - Symptoms, variability in lung function, and airway hyperresponsiveness are decreased by ICS, so it is often more difficult to confirm the diagnosis after controller treatment is started
- The flow-chart (Box 1-1) has been updated in 2022 to emphasize the different approach for *initial* diagnosis compared with confirming the diagnosis in patients taking controller treatment
  - Diagnostic approaches for patients taking controller treatment are in Boxes 1-3 and 1-4
- At a global level, spirometry before and after bronchodilator is the most useful initial investigation
  - Optimize the conditions for testing, if possible (e.g. when symptomatic, and after withholding bronchodilators)
  - In patients on controller treatment, more than one test is often needed
- GINA will review GRADE evidence from ERS Task Force on diagnosis of asthma *(Louis et al, ERJ 2022)*

Diagnosis of asthma



Diagnosis in patients already on controller treatment

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2) and review controller treatment (Box 3-5).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 hrs for SABA, 24 hrs for twice-daily ICS-LABA, 36hrs for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-5). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1-5). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist. 'Variable airflow limitation' refers to expiratory airflow.

Diagnosis of asthma in low- and middle-income countries

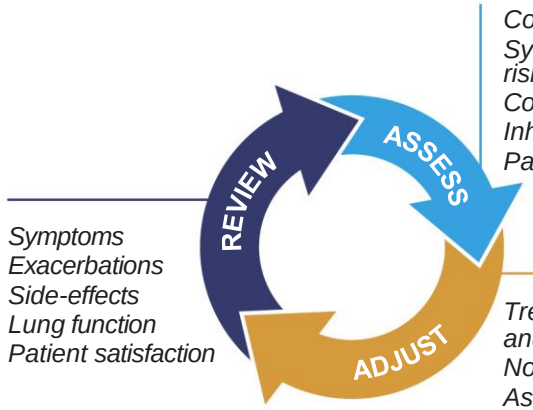
- Asthma is often under-diagnosed
  - Differential diagnosis often includes other endemic respiratory disease, e.g. tuberculosis, HIV/AIDS-associated lung disease, parasitic or fungal lung diseases
  - A syndromic approach is often used for diagnosis
- GINA recommends confirmation of asthma diagnosis with lung function testing, whenever possible, before commencing long-term treatment
  - Spirometry-based testing if available
  - Peak expiratory flow (PEF)
    - >20% increase in PEF, 15 minutes after 2 puffs of salbutamol = asthma likely (WHO-PEN)
    - Improvement of symptoms and PEF after 4 weeks ICS treatment
- Access to affordable diagnostic equipment and skills training needs to be substantially scaled up in low- and middle-income countries

GINA treatment figure for adults and adolescents (≥12 years)

- Treatment options are shown in two tracks
  - This was necessary to clarify how to step treatment up and down with the same reliever
- **Track 1, with low dose ICS-formoterol as the reliever, is the preferred strategy**
  - Preferred because of the evidence that using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and lung function
- **Track 2, with SABA as the reliever, is an 'alternative' (non-preferred) strategy**
  - Less effective than Track 1 for reducing severe exacerbations
  - Use Track 2 if Track 1 is not possible; can also consider Track 2 if a patient has good adherence with their controller, and has had no exacerbations in the last 12 months
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to continue to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- "Other controller options"
  - These have limited indications, or less evidence for efficacy and/or safety than Track 1 or 2 options
- Step 5
  - A new class of biologic therapy has been added (anti-TSLP)
  - A prompt added about the GINA severe asthma guide

Adults & adolescents 12+ years

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



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

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

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

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

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

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

	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. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

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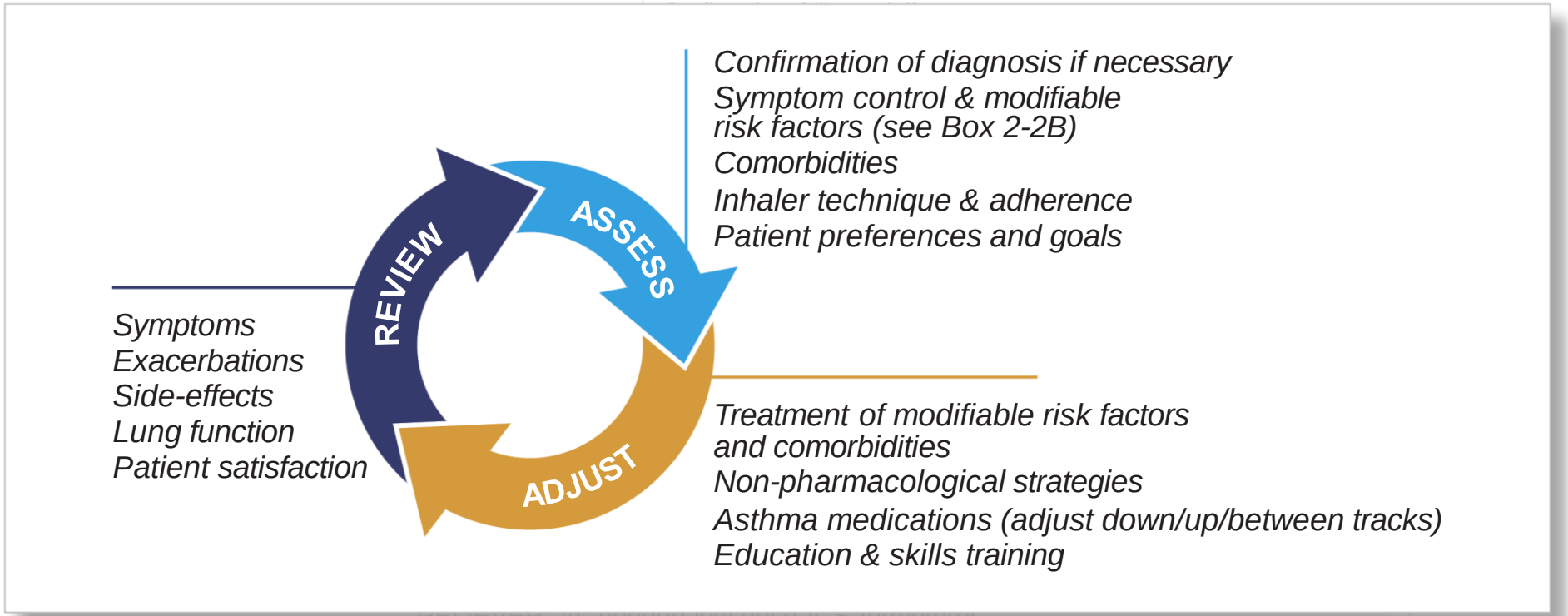

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(Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol

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

STEP 1	STEP 2	STEP 3	Medium/high dose maintenance ICS-LABA	Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA		

RELIEVER: As-needed short-acting beta$_2$-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

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CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol

STEPS 1 – 2
As-needed low dose ICS-formoterol

STEP 3
Low dose maintenance ICS-formoterol

STEP 4
Medium dose maintenance ICS-formoterol

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R,

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

STEP 1
Take ICS whenever SABA taken

STEP 2
Low dose maintenance ICS

STEP 3
Low dose maintenance ICS-LABA

STEP 4
Medium/high dose maintenance ICS-LABA

STEP 5
Add-on LAMA
Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP

RELIEVER: As-needed short-acting beta$_2$-agonist

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

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	STEPS 1 – 2	STEP 3	STEP 4	STEP 5
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	RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
CONTROLLER and **ALTERNATIVE RELIEVER**		Low dose	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE,

Other controller options for either track (limited indications, or less evidence for efficacy or safety)					
	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. As last resort consider adding low dose OCS but consider side-effects*

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
  - 15–27% of adults dying of asthma

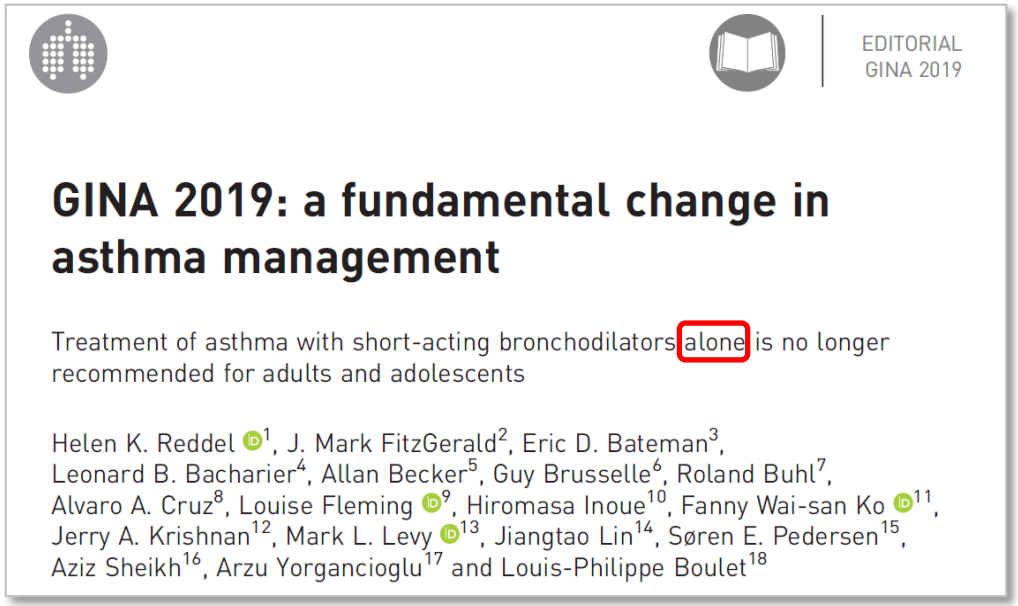
  } had symptoms less than weekly in previous 3 months *(Dusser, Allergy 2007; Bergstrom, 2008)*

- Exacerbation triggers are unpredictable (viruses, pollens, pollution, poor adherence)
- Even 4–5 lifetime OCS courses increase the risk of osteoporosis, diabetes, cataract *(Price et al, J Asthma Allerg 2018)*

SABA: short-acting beta$_2$-agonist

Why not treat with SABA alone?

- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Asthma was thought to be a disease of bronchoconstriction
  - Role of SABA reinforced by rapid relief of symptoms and low cost
- Regular use of SABA, even for 1–2 weeks, is associated with increased AHR, reduced bronchodilator effect, increased allergic response, increased eosinophils *(e.g. Hancox, 2000; Aldridge, 2000)*
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA associated with ↑ exacerbations and ↑ mortality *(e.g. Suissa 1994, Nwaru 2020)*
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
- The only previous option was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available



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 FitzGerald[2], Eric D. Bateman[3], Leonard B. Bacharier[4], Allan Becker[5], Guy Brusselle[6], Roland Buhl[7], Alvaro A. Cruz[8], Louise Fleming[9], Hiromasa Inoue[10], Fanny Wai-san Ko[11], Jerry A. Krishnan[12], Mark L. Levy[13], Jiangtao Lin[14], Søren E. Pedersen[15], Aziz Sheikh[16], Arzu Yorgancioglu[17] and Louis-Philippe Boulet[18]

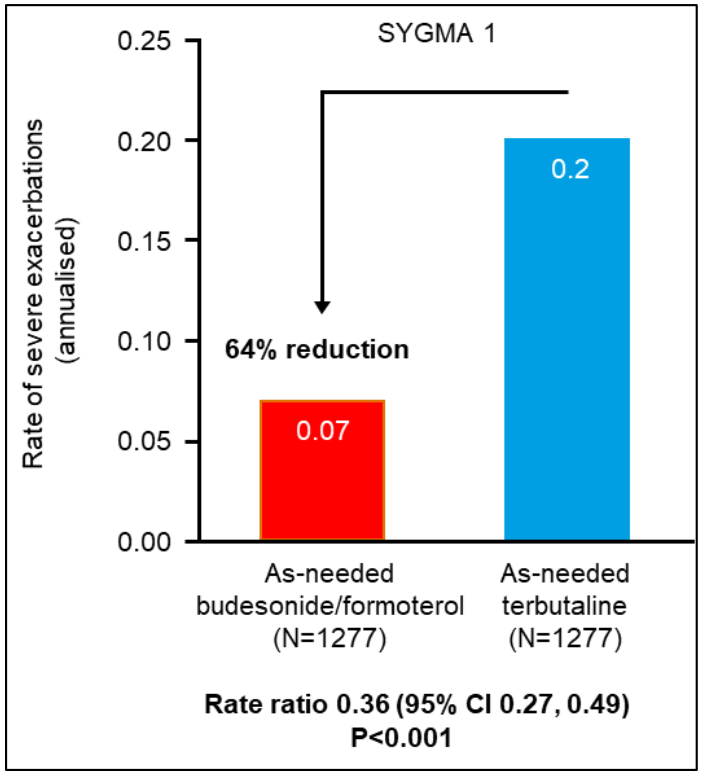
As-needed low dose ICS-formoterol in mild asthma (n=9,565)

COMPARED WITH AS-NEEDED SABA

- The risk of severe exacerbations was reduced by 60–64% (SYGMA 1, Novel START)

COMPARED WITH MAINTENANCE LOW DOSE ICS

- The risk of severe exacerbations was similar (SYGMA 1 & 2), or lower (Novel START, PRACTICAL)
- Small differences in other asthma outcomes, favoring maintenance ICS, but all were less than the minimal clinically important difference
  - ACQ-5 mean difference 0.15 (MCID 0.5)
  - FEV_1 mean difference ~54 mL
  - FeNO mean difference ~10ppb (Novel START, PRACTICAL)
  - No evidence of progressive worsening over 12 months
- In Novel START and PRACTICAL, outcomes were independent of baseline features including blood eosinophils, FeNO, lung function, and exacerbation history
- Average ICS dose was ~50–100mcg budesonide/day

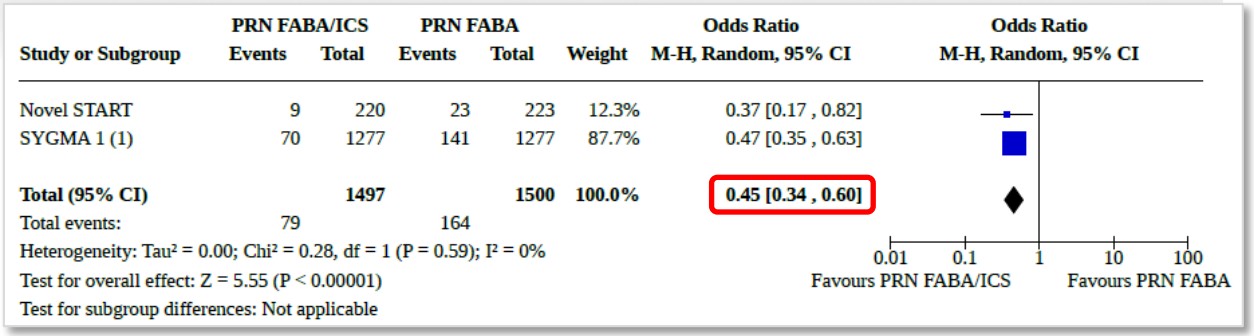


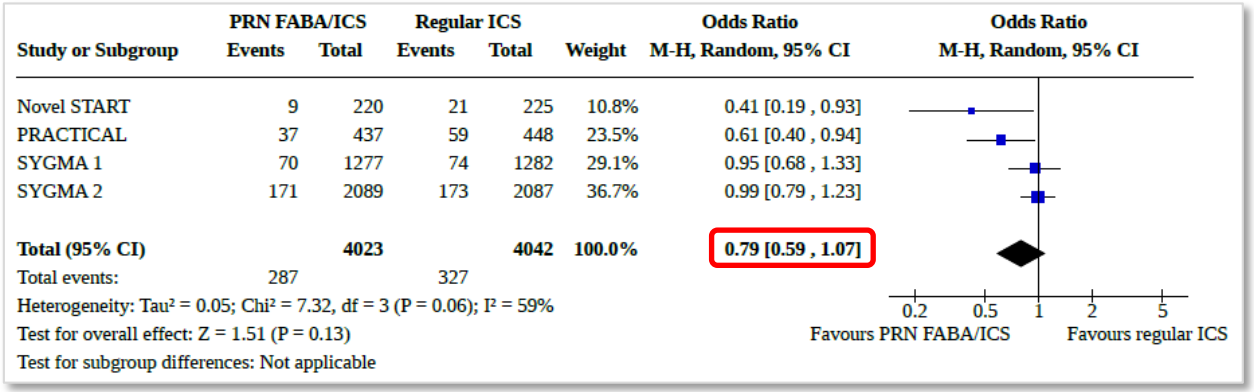
O'Byrne et al, NEJM 2018

*Budesonide-formoterol 200/6 mcg, 1 inhalation as needed for symptom relief

New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of all four RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA





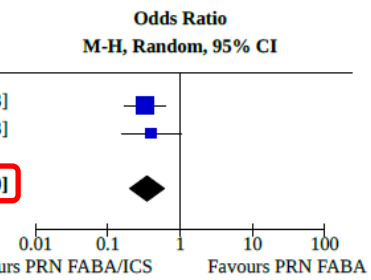
New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS

Analysis 1.3. Comparison 1: As required fixed dose combination inhaler versus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit

Study or Subgroup	PRN FABA/ICS Events	PRN FABA/ICS Total	PRN FABA Events	PRN FABA Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START (1)	13	220	36	223	67.2%	0.33 [0.17 , 0.63]
SYGMA 1	6	1277	15	1277	32.8%	0.40 [0.15 , 1.03]
Total (95% CI)		**1497**		**1500**	**100.0%**	**0.35 [0.20 , 0.60]**
Total events:	19		51			

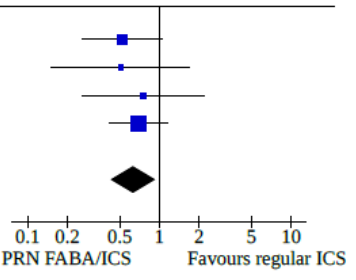
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Fixed dose combination inhaler as required versus regular inhaled steroid plus as required short acting beta agonist, Outcome 3: Exacerbations requiring hospital admission or emergency department / urgent care visit

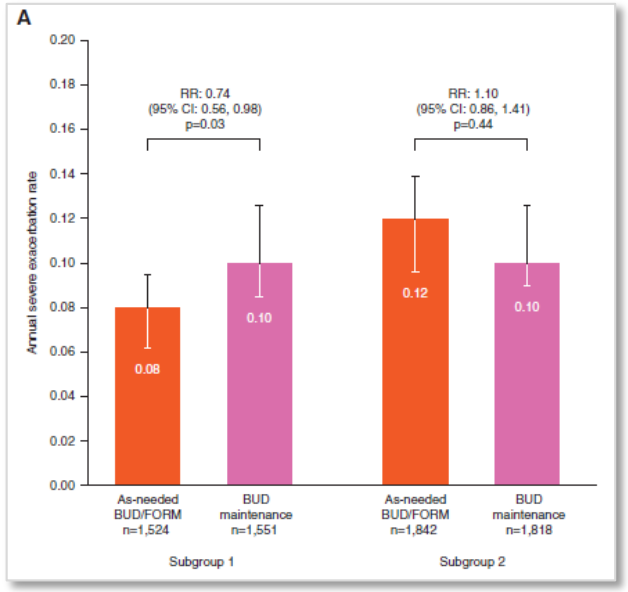
Study or Subgroup	PRN FABA/ICS Events	PRN FABA/ICS Total	Regular ICS Events	Regular ICS Total	Weight	Odds Ratio M-H, Random, 95% CI
Novel START	13	220	24	225	27.4%	0.53 [0.26 , 1.06]
PRACTICAL	4	437	8	448	9.3%	0.51 [0.15 , 1.70]
SYGMA 1	6	1277	8	1282	12.0%	0.75 [0.26 , 2.17]
SYGMA 2	25	2089	36	2087	51.3%	0.69 [0.41 , 1.15]
Total (95% CI)		**4023**		**4042**	**100.0%**	**0.63 [0.44 , 0.91]**
Total events:	48		76			

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.47 (P = 0.01)
Test for subgroup differences: Not applicable

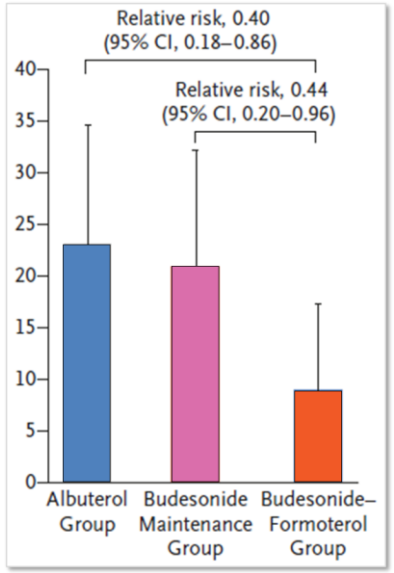


New evidence for as-needed ICS-formoterol in mild asthma

- Meta-analysis of four all RCTs, n=9,565
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - ED visits or hospitalizations
    - 65% lower than with SABA alone
    - 37% lower than with daily ICS
- Analysis by previous treatment
  - Patients taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA *(Bateman, Annals ATS 2021; Beasley, NEJMed 2019)*



Bateman 2021

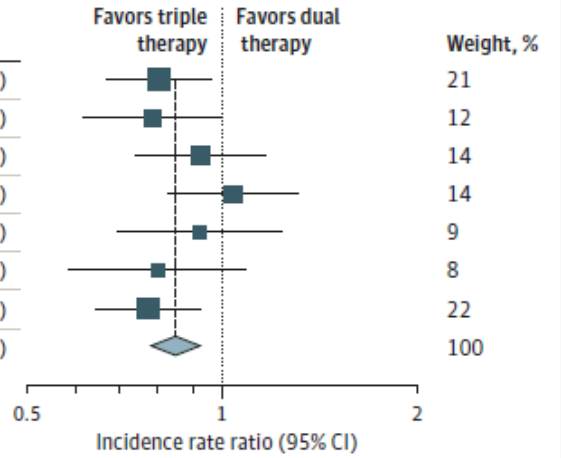


Beasley 2019

Other changes in medication recommendations for ≥12 years

- Long-acting muscarinic antagonists (LAMA) should not be used as monotherapy for asthma (i.e. without ICS) because of increased risk of severe exacerbations *(Baan, Pulm Pharmacol Ther 2021)*
- Adding LAMA to ICS-LABA: GRADE review and meta-analysis *(Kim, JAMA 2021)* confirms previous findings
  - Small increase in lung function (mean difference 0.08 L)
  - No clinically important benefits for symptoms or quality of life → don't prescribe for dyspnea
  - Modest overall reduction in exacerbations compared with ICS-LABA (risk ratio 0.83 [0.77, 0.90])

Source	Mean annualized exacerbation rate[a] Triple	Dual	Incidence rate ratio (95% CI)
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)



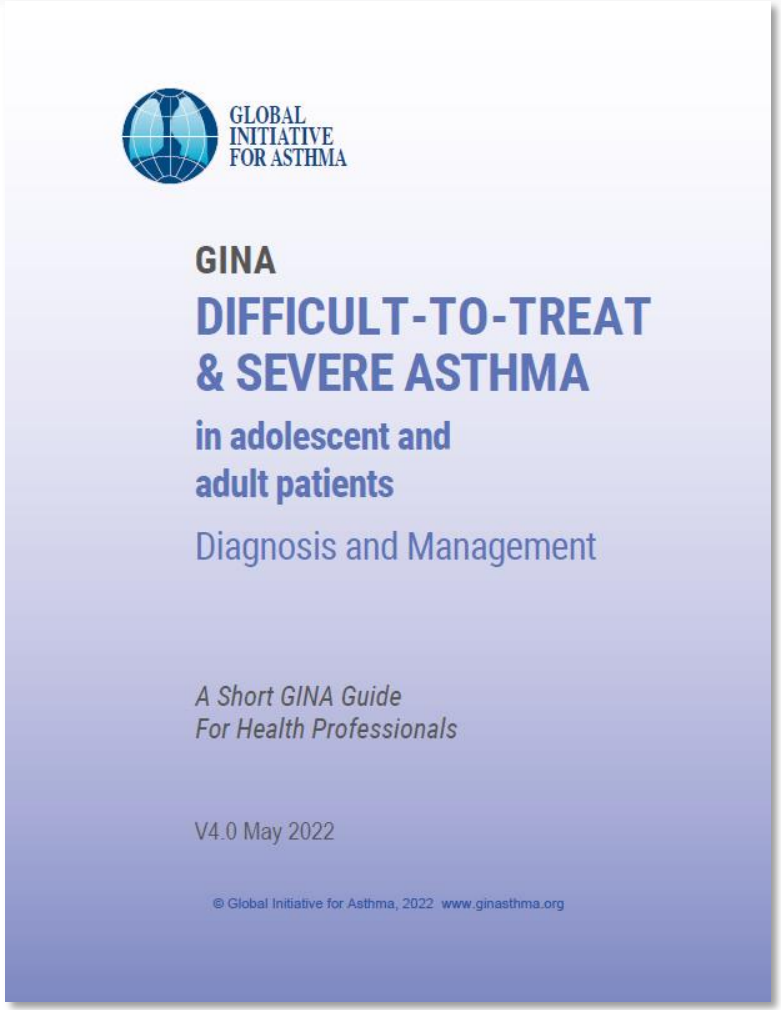
  - Patients with exacerbations should receive at least medium dose ICS-LABA before considering add-on LAMA
- Chromone pMDIs (sodium cromoglycate, nedocromil sodium) have been discontinued globally

Management of asthma in low- and middle-income countries

- 96% of asthma deaths are in low- and middle-income countries (LMIC) *(Meghji, Lancet 2021)*
  - Much of this burden is avoidable, especially with ICS *(e.g. Comaru, Respir Med 2016)*
  - Barriers include lack of access to essential medications, and prioritization of acute care over chronic care by health systems *(Mortimer, ERJ 2022)*
- Lack of access to affordable quality-assured inhaled medications *(Stolbrink, review for WHO 2022)*
  - Oral bronchodilators have slow onset of action and more side-effects than inhaled
  - OCS are associated with serious cumulative adverse effects (e.g. sepsis, cataract, osteoporosis) even with occasional courses *(Price, J Asthma Allerg 2018)*
- GINA supports the initiative by IUATLD towards a World Health Assembly Resolution on equitable access to affordable care for asthma, including inhaled medicines
  - In the meantime, if Track 1 is not available due to lack of access or affordability, Track 2 treatment may be preferable, although less effective in reducing exacerbations
  - If Track 2 options also not available, taking ICS whenever SABA is taken may be preferable to LTRA or maintenance OCS because of concerns about efficacy and/or safety
  - Greatest overall benefit at a population level would be from increasing access to ICS-formoterol

Short GINA guide for difficult-to-treat and severe asthma in adults and adolescents, 2022

- Full size rather than ‘pocket’ size; easier to read
- Updated decision tree for assessment of adults and adolescents with difficult-to-treat asthma
  - Sections 1–4: primary or specialist care
  - Sections 5–8: specialist care
  - Sections 9–10: ongoing collaborative care with patient, GP, specialist, other health professionals
- Decision tree and text are also included in full GINA report (Chapter 3E)
- Slide set on GINA website



Key changes to GINA severe asthma guide in 2022

- Additional investigations
  - Consider screening for adrenal insufficiency if patient is on maintenance OCS or high dose ICS-LABA
  - For patients with eosinophils ≥300/µl, investigate for non-asthma causes including *Strongyloides* (often asymptomatic), before considering biologic therapy
  - For patients with hypereosinophilia, e.g. ≥1500/µl, investigate for conditions such as EGPA
- Assessment of inflammatory phenotype
  - If blood eosinophils or FeNO not elevated, repeat up to 3 times, at least 1–2 weeks after stopping OCS, or on lowest possible OCS dose
- Treatment options for patients with no evidence of Type 2 inflammation on repeated testing
  - Consider add-on treatment with LAMA or low-dose azithromycin if not already tried
  - Can also consider anti-IL4R* (if on maintenance OCS) or anti-TSLP* (but insufficient evidence with maintenance OCS)
- Consider maintenance OCS only as last resort, because of serious cumulative adverse effects

**Check local eligibility criteria for specific biologic therapies*

Key changes to GINA severe asthma guide in 2022 (continued)

- Anti-IL4R* (dupilumab) for severe eosinophilic/Type 2 asthma
  - Not suggested if blood eosinophils (current or historic) >1500/µl
  - Dupilumab now also approved for children ≥6 years with severe eosinophilic/Type 2 asthma, not on maintenance OCS *(Bacharier, NEJMed 2021)*
- Anti-TSLP* (tezepelumab) now approved for severe asthma (age ≥12 years)
  - Greater clinical benefit with higher blood eosinophils and/or higher FeNO
  - Insufficient evidence in patients taking maintenance OCS

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypereosinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or maintenance OCS	Moderate-severe atopic dermatitis, CRSwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	Severe asthma	

**Check local eligibility criteria for specific biologic therapies; TSLP: thymic stromal lymphopoietin*

GP OR SPECIALIST CARE

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

Consider referring to specialist or severe asthma clinic at any stage

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

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

1 Confirm the diagnosis (asthma/differential diagnoses)

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

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

3 Optimize management, including:

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

4 Review response after ~3-6 months

Is asthma still uncontrolled?

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

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

Does asthma become uncontrolled when treatment is stepped down?

yes → Restore previous dose

no → Continue optimizing management

Key

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

Assess and treat severe asthma phenotypes

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

5 *Investigate* further and provide *patient support*

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

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

yes

Type 2 airway inflammation

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

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

yes

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

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

Go to section **10**

no

Type 2 inflammation

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

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

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

no

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

Not currently eligible for T2-targeted biologic therapy

Go to section **10**

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

Assess and treat severe asthma phenotypes *cont'd*

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

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

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

Which biologic is appropriate to start first?

Eligibility | *Predictors of asthma response*

Anti-IgE *(omalizumab)*

*Is the patient eligible for **anti-IgE** for severe allergic asthma?**
- Sensitization on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

What factors may predict good asthma response to anti-IgE?
- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

no / *no*

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

*Is the patient eligible for **anti-IL5 / anti-IL5R** for severe eosinophilic asthma?**
- Exacerbations in last year
- Blood eosinophils, e.g. ≥150/µl or ≥300/µl

What factors may predict good asthma response to anti-IL5/5R?
- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

no / *no*

Anti-IL4R *(dupilumab)*

*Is the patient eligible for **anti-IL4R** for severe eosinophilic/Type 2 asthma?**
- Exacerbations in last year
- Blood eosinophils ≥150 and ≤1500/µl, or FeNO ≥25 ppb, or taking maintenance OCS

What factors may predict good asthma response to anti-IL4R?
- Higher blood eosinophils +++
- Higher FeNO +++

no / *no*

Anti-TSLP *(tezepelumab)*

*Is the patient eligible for **anti-TSLP** for severe asthma?**
- Exacerbations in last year

What factors may predict good asthma response to anti-TSLP?
- Higher blood eosinophils +++
- Higher FeNO +++

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

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

*Good asthma response?**

unclear → Extend trial to 6-12 months*

yes → Good response to T2-targeted therapy

no → **STOP add-on**

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

no → Little/no response to T2-targeted therapy

No evidence of Type 2 airway inflammation

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

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

Monitor / Manage severe asthma treatment

Continue to optimize management

9 Review response

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

If good response to Type 2-targeted therapy

yes

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

If no good response to Type 2-targeted therapy

no

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

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

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

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

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

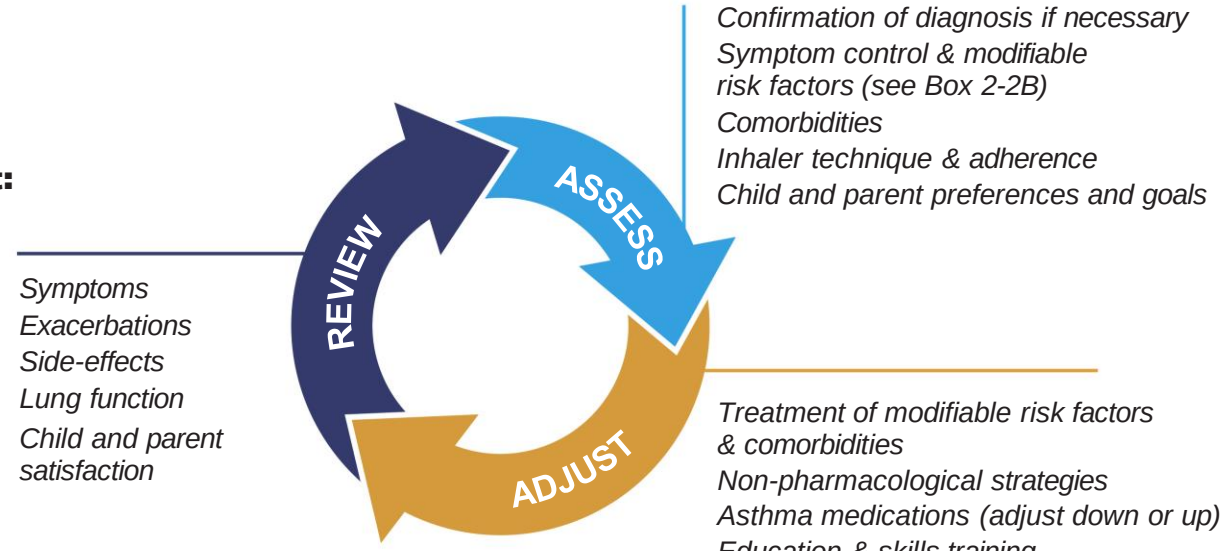
Notes:

Changes to treatment figure in children 6–11 years (Box 3-5B)

- "Other controller options" clarified
  - These therapies may have limited indications, or less evidence about efficacy and/or safety than the "preferred" treatment options
- Step 5:
  - Anti-IL4R (dupilumab) now approved for children with severe eosinophilic/Type 2 asthma (not on maintenance OCS)
  - Consider maintenance OCS only as last resort

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review



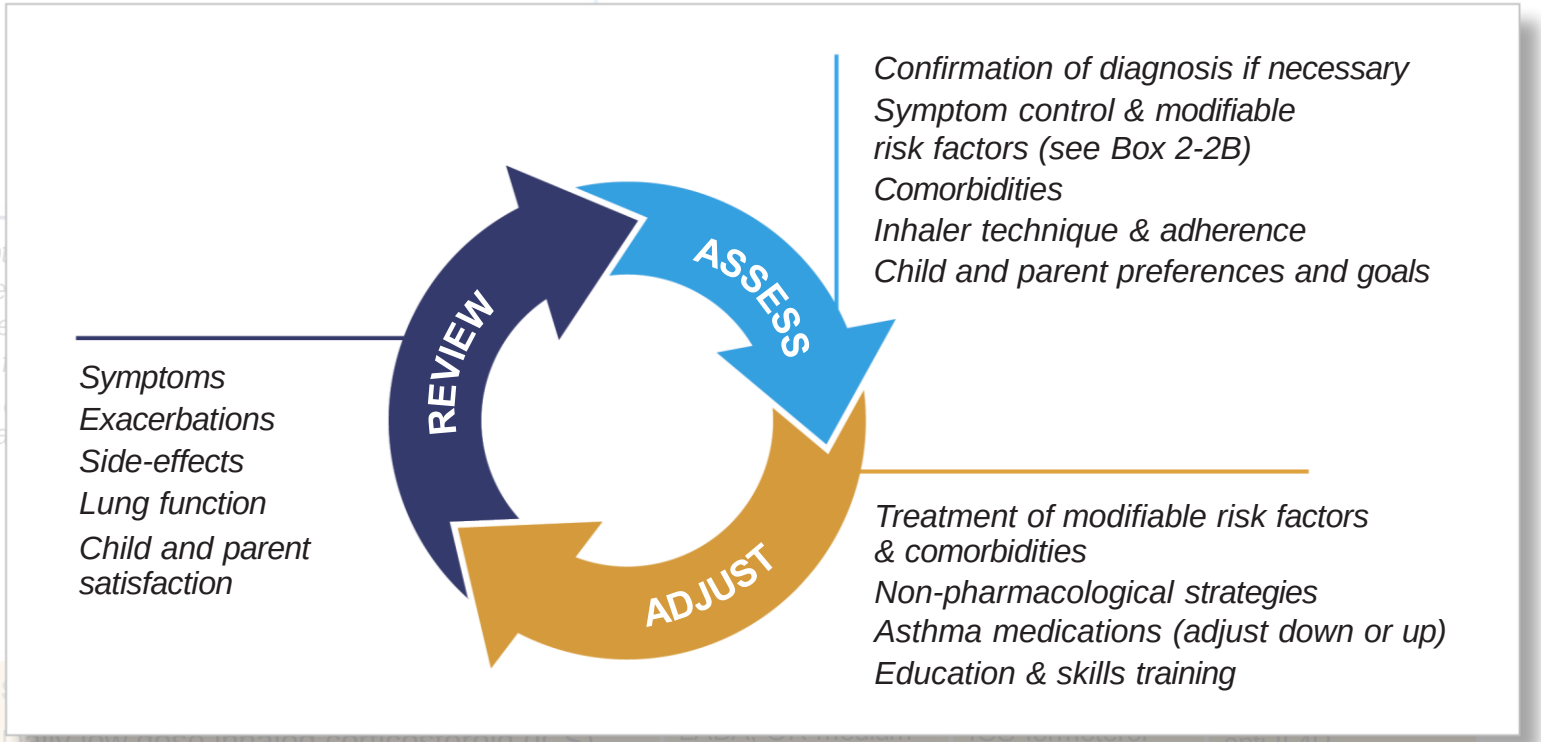
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	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, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*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, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review



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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	maintenance and reliever therapy (MART). Refer for expert advice	anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*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, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken				
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*				
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)			
Other controller options (limited indications, or less evidence for efficacy or safety)		*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*			
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms			Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)		
Other controller options (limited indications, or less evidence for efficacy or safety)			*Low dose ICS + LTRA*		
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms				**STEP 4** Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	
Other controller options (limited indications, or less evidence for efficacy or safety)				*Add tiotropium or add LTRA*	
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

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

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms					Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)					*Add-on anti-IL5 or, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

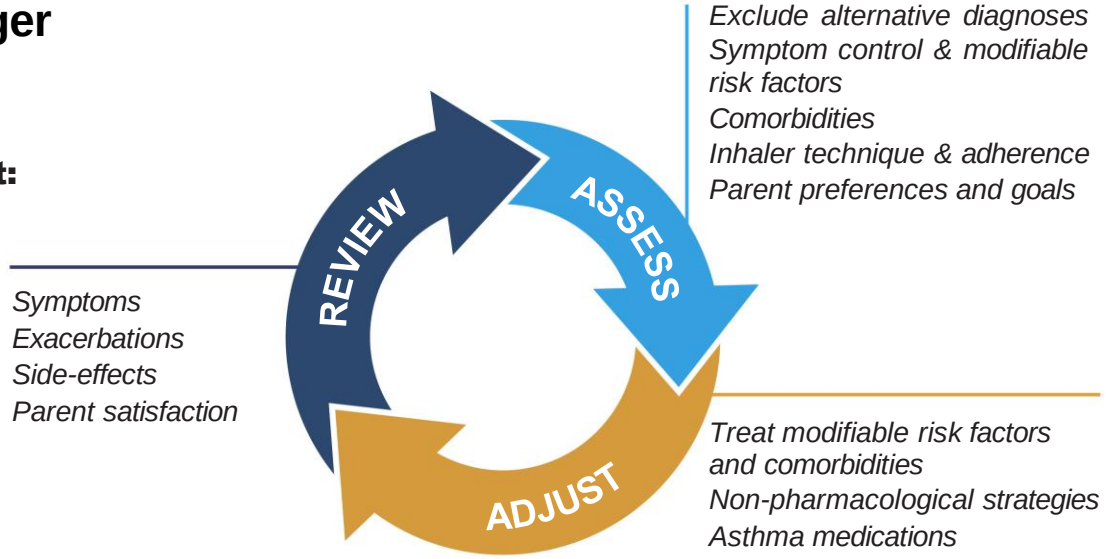
**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Changes to treatment figure in children 5 years and younger (Box 6-5)

- Management of wheezing episodes in pre-school children with no (or few) interval symptoms
  - Intermittent short course ICS added to Step 1 for consistency with the existing text (Chapter 6, part C)
  - Only consider this option if confident it will be used appropriately, because of the risk of side-effects

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response

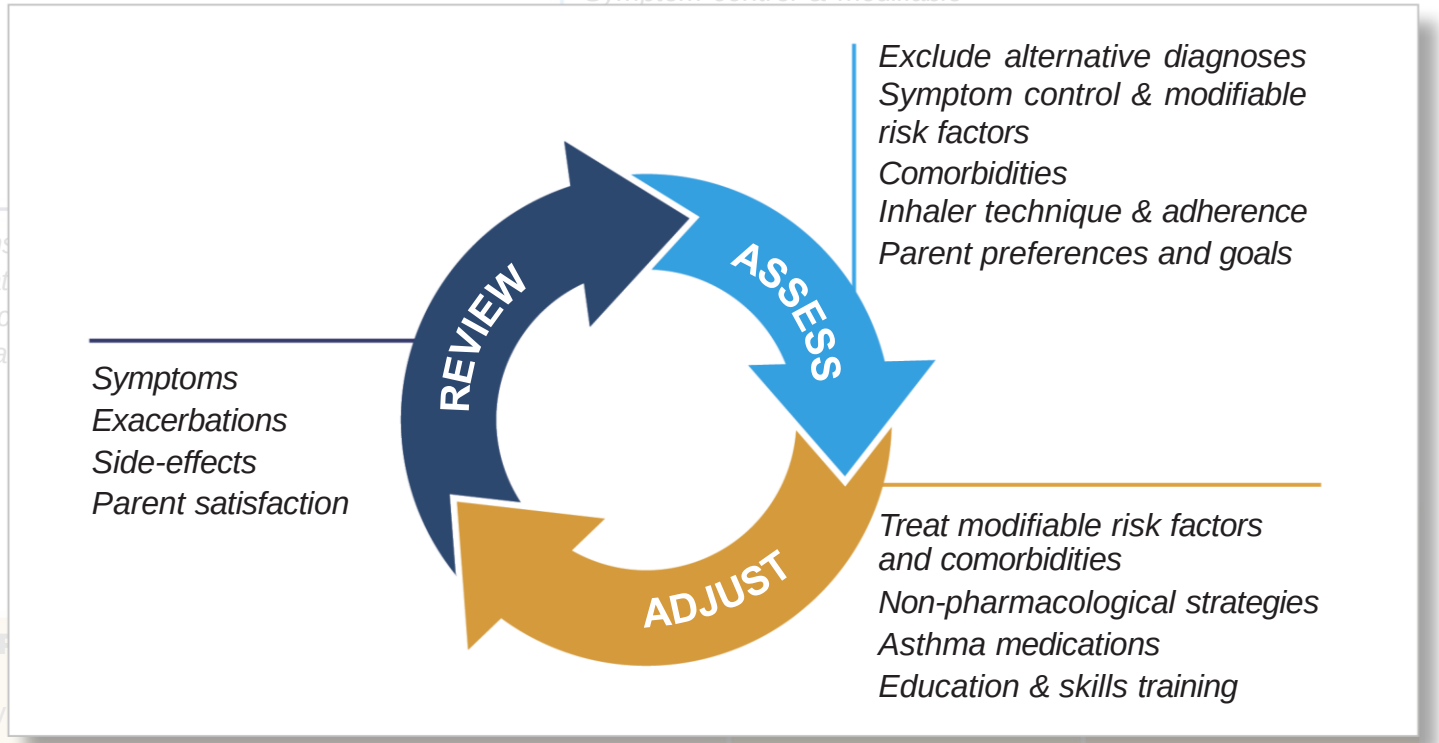


Asthma medication options:
Adjust treatment up and down for individual child's needs

	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 (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course 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 beta$_2$-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. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



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

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily (see table of ICS dose ranges for pre-school children)		
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course 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 beta$_2$-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. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS	Asthma not well-controlled on double ICS
			Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response

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

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

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE				
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*			
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms			

symptoms

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

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response

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

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

	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)		
Other controller options (limited indications, or less evidence for efficacy or safety)		*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*		
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:		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. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.		

symptoms

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

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response

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

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

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE			Double 'low dose' ICS	
Other controller options (limited indications, or less evidence for efficacy or safety)			*Low dose ICS + LTRA Consider specialist referral*	
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:			Asthma diagnosis, and asthma not well-controlled on low dose ICS	
			Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	

symptoms

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

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response

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

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

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE				Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)				*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:				Asthma not well-controlled on double ICS

Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures

symptoms

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

Definition of asthma severity and mild asthma

- By the ATS/ERS Task Force definition, asthma severity is assessed retrospectively from the treatment required to control the patient's asthma, i.e. after at least several months of treatment *(Taylor, ERJ 2008; Reddel, AJRCCM 2009)*
  - By this definition, asthma severity can be assessed only when treatment has been optimized and asthma is well-controlled, except for patients taking high dose ICS-LABA
- 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 *(Chung, ERJ 2014)*
  - This definition is widely accepted, and has clinical utility
  - Severe asthma is distinguished from 'difficult-to-treat' asthma that is difficult to treat because of problems such as poor adherence, incorrect inhaler technique and comorbidities
- Mild asthma is currently defined as asthma that is well controlled on low dose ICS or as-needed-only ICS-formoterol
  - The utility and relevance of this definition is much less clear
  - The term 'mild asthma' is often interpreted very differently
  - Patients and clinicians often assume that 'mild asthma' means no risk and no need for controller treatment
  - BUT: up to 30% asthma deaths are in patients with infrequent symptoms *(Dusser, Allergy 2007; Bergstrom, Respir Med 2008)*

Interim advice about asthma severity descriptors

1. Severe asthma: GINA continues to support the current definitions of severe asthma, and difficult-to-treat asthma
2. 'Mild asthma': GINA suggests that this term should generally be avoided in clinical practice if possible, because it is used and interpreted in different ways
   - If used, emphasize importance of ICS-containing treatment to reduce risk of severe or fatal exacerbations
3. For population-level observational studies: report the controller and reliever treatment not the 'Step', and don't impute severity
   - e.g. 'patients prescribed low dose ICS-LABA with as-needed SABA', not 'Step 3 patients' and not 'moderate asthma'
4. For clinical trials: describe the included patients by their asthma control and treatment (controller and reliever), and don't impute severity
5. GINA proposes holding a stakeholder discussion about the definition of mild asthma, to obtain agreement about the implications for clinical practice and clinical research of the changes in knowledge about asthma pathophysiology and treatment since the current definition of asthma severity was published

Other changes or clarifications in GINA 2022

- "Written" asthma action plans
  - Handwritten, printed, digital or pictorial instructions about what to do when asthma gets worse
  - Not just verbal instructions!
- Acute asthma in healthcare settings
  - At present, salbutamol (albuterol) is the usual bronchodilator in acute asthma management
  - Formoterol has similar efficacy and safety in ED studies *(Rodrigo, Ann Allerg Asthma Immunol, 2010)*
  - One study showed high dose budesonide-formoterol had similar efficacy and safety as SABA *(Balanag, Pulm Pharmacol Ther 2006)*
  - Patients admitted to hospital for an asthma exacerbation should continue, or commence, ICS-containing therapy
- Air filters can reduce fine particle exposure, but no consistent effect on asthma outcomes *(Park, Allergy Asthma Immunol Res 2021)*
- Use of e-cigarettes is associated with increased risk of respiratory symptoms and asthma exacerbations *(Cho, PLoSOne 2016; Wills, ERJ 2021)*

GINA guidance about COVID-19 and asthma

Updated 30 April 2022

GINA Global Strategy for Asthma Management and Prevention

www.ginasthma.org

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, studies to date indicate that people with well-controlled asthma are not at increased risk of COVID-19-related death *(Williamson, Nature 2020; Liu et al JACI IP 2021)* and in one meta-analysis, mortality appeared to be lower than in people without asthma *(Hou, JACI IP 2021).*
  - However, the risk of COVID-19 death was increased in people who had recently needed OCS for their asthma *(Williamson, Nature 2020; Shi, Lancet RM 2022)* and in hospitalized patients with severe asthma *(Bloom, Lancet RM 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 2020–21, many countries saw a *decrease* in asthma exacerbations and influenza-related illness
  - The reasons are not precisely known, but may be due to public health measures such as handwashing, masks and social/physical distancing that reduced the incidence of other respiratory infections, including influenza *(Davies, Thorax 2021)*

COVID-19 and asthma medications

- Advise patients to continue taking their prescribed asthma medications, particularly inhaled corticosteroids
  - For patients with severe asthma, continue biologic therapy or OCS if prescribed
- Are inhaled corticosteroids (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
- When COVID-19 is confirmed or suspected, or local risk is moderate or high, avoid nebulizers where possible, to reduce the risk of spreading virus to health professionals and other patients/family
  - For bronchodilator administration, pressurized metered dose inhaler via a spacer is preferred except for acute severe asthma
  - Add a mouthpiece or mask to the spacer if required

COVID-19 and asthma – infection control

- In healthcare facilities, follow local COVID-19 testing recommendations and infection control procedures if spirometry or peak flow measurement is needed *(e.g. Virant, JACI in Practice 2022)*
  - Use of an in-line filter minimizes the risk of transmission *during* spirometry, but many patients cough *after* performing spirometry; coach the patient to stay on the mouthpiece if they feel the need to cough
  - If spirometry is not available due to local infection control restrictions, and information about lung function is needed, consider asking patients to monitor lung function at home
- Follow local infection control procedures if other 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
- Are COVID-19 vaccines safe in people with allergies?
  - In general, allergic reactions to vaccines are rare
  - Patients with a history of severe allergic reaction to a COVID-19 vaccine ingredient (e.g. polyethylene glycol for Pfizer/BioNTech or Moderna, or polysorbate 80 for AstraZeneca or J&J/Janssen), should receive a different COVID-19 vaccine. More details from ACIP are here
  - People with allergies to food, insect venom or other medications can safely receive COVID-19 vaccines
  - As always, patients should speak to their healthcare provider if they have concerns
  - Follow local advice about monitoring patients after COVID-19 vaccination
- 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
- Based on the risks and benefits, and with the above precautions, GINA recommends people with asthma should be up to date with COVID-19 vaccination (including booster doses, if available)

COVID-19 vaccines and asthma

- COVID-19 vaccination and biologic therapy
  - We suggest that the first dose of asthma 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
- Influenza vaccination
  - Remind people with asthma to have an annual influenza vaccination
  - CDC now recommends that influenza vaccine and COVID-19 vaccine can be given on the same day
- After COVID-19 vaccination
  - Current advice from the United States Centers for Disease Control and Prevention (CDC) is that where there is substantial transmission of COVID-19, people will be better protected, even if they are fully vaccinated, if they wear a mask in indoor public settings; this will also reduce risk to others. Further details are here
- GINA will update advice about COVID-19 and asthma as new data become available

Topics to be addressed in future GINA reports

(Some were delayed from 2021 by COVID-19)

- Allergen immunotherapy for asthma
- Diagnosis, assessment and management of asthma in children 5 years and younger
- Further discussion about the definition of mild asthma, and assessment of symptom control
- Use of digital tools and communication in asthma management
- A pocket guide on management of severe asthma in children 6–11 years is in development
- Advice about COVID-19 and asthma will be updated as relevant new information emerges

- We will be seeking your feedback on how to improve GINA resources