

Asthma: Quick-Relief (Short-Acting) Medications Washington Drug Archive Report

Washington P&T Committee

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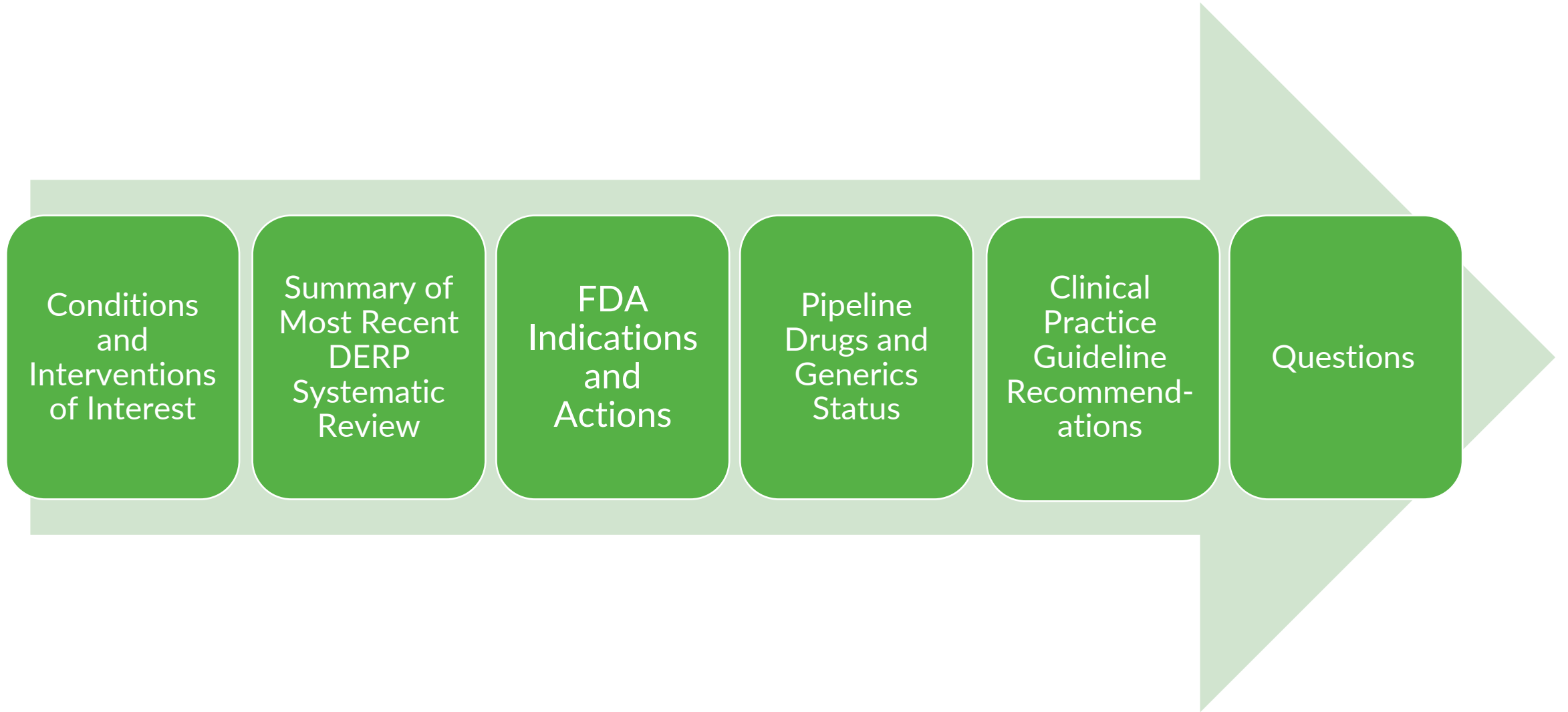


Aim of Project

- The Drug Effectiveness Review Project (DERP) aims to present information to the Washington State Pharmacy and Therapeutics (P&T) Committee with topic reports on 9 drug classes that are candidates to be archived from active review by the Committee
- The 9 drug classes identified by the Washington Health Care Authority (HCA) as archive candidates are:
 - Anticoagulants
 - Antiemetics
 - Antiplatelets
 - Asthma controllers
 - **Asthma quick relief drugs**
 - Long-acting opioids
 - Overactive bladder drugs
 - PCSK9 inhibitors
 - Statins

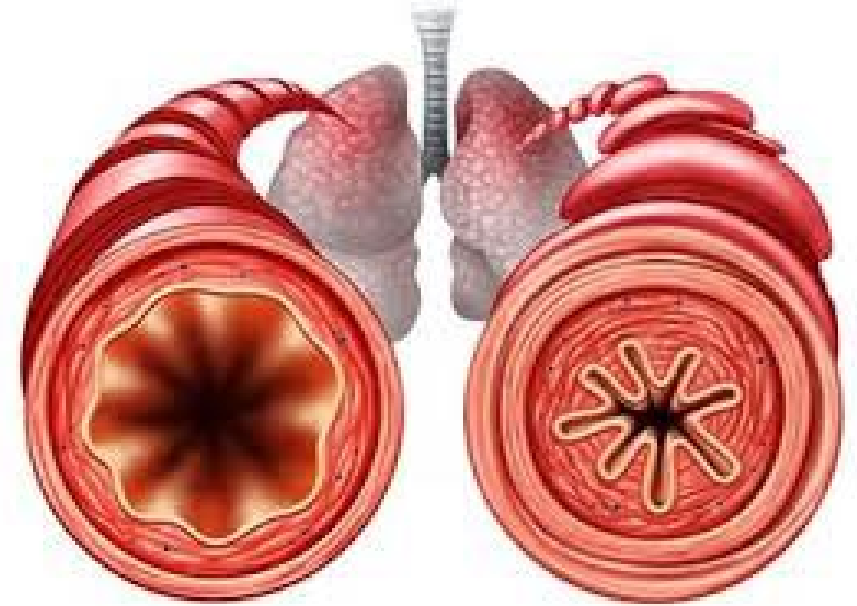
*Drug classes in **green** are presented in this report*

Overview



Asthma: Definition

- Asthma is a chronic inflammatory disorder of the lungs; this inflammation can cause:
 - ❑ Reversible airway obstruction (spontaneous reversal or with treatment)
 - ❑ Increased airway responsiveness
- Symptoms include:
 - ❑ Wheezing
 - ❑ Shortness of breath
 - ❑ Coughing
 - ❑ Chest tightness
- Long-term risks of severe asthma include:
 - ❑ Deterioration of lung function
 - ❑ Side effects of long-term medications such as oral corticosteroids



Source. www.urmc.rochester.edu

Asthma: Epidemiology

- Nearly [25 million individuals](#) (about 1 in 12) in the US have asthma
 - 3% to 13% have [severe asthma](#)
 - Asthma has the highest chronic disease prevalence in children (6.5%)
 - Male children are more likely to have asthma than female children, but this is reversed in adults
 - Non-Hispanic Black children are twice as likely to have asthma compared with White children
 - Exercise-induced asthma (bronchoconstriction) occurs in 5% to 30% of the general population; up to 90% of people with asthma have this symptom

Risk Factors for [Asthma](#)

- Family history/genetics
- Allergies
- Viral respiratory infections during childhood

- Occupational exposures
- Environmental exposures
 - Smoking
 - Air pollution
- Obesity

Treatments for Asthma

- No cure for asthma, but goal of treatment is to mitigate symptoms, prevent exacerbations, and reduce long-term complications
- Asthma is classified by whether symptoms are intermittent versus persistent, and then by symptom severity

Nonpharmacologic treatments

- Breathing exercises
- Increased physical activity
- Avoiding environmental triggers

Pharmacologic agents

- Quick-relief medications (bronchodilators)
- Controller medications
- Combination quick-relief and controller medications (newly approved/emerging market)
- Biologics (newer treatments for severe asthma, including omalizumab, mepolizumab, reslizumab)

Summary of Most Recent DERP Products (Quick Relief)

Last Report	2008
Date Presented	August 2008
Report Title	<i>Quick-Relief Medications for Asthma</i>
Search Dates	From inception (most databases) through June 2, 2008
Authors	Oregon Evidence-based Practice Center and CEbP researchers
<u>Surveillance</u> Since Last Report	
2015 scan	<i>Quick-Relief Medications for Asthma</i> • Search Dates: October 2013 through December 22, 2014
3 additional scans from 2009 to 2013	<i>Quick-Relief Medications for Asthma</i>

PICOS of Most Recent DERP Report (Quick Relief)

- *Population*

- Adults and children with asthma, including those with exercise-induced bronchospasm (in outpatient settings, including urgent care and emergency department)

- *Comparators*

- Another listed intervention (head-to-head)

- *Study Designs*

- Randomized controlled trials (RCTs) and nonrandomized controlled trials with at least 20 participants
- Observational studies for safety outcomes only

PICOS of Most Recent DERP Report (Quick Relief)

- *Interventions*

Name	Brand Name	FDA Approval Date	Formulation (Delivery)
Short-acting beta agonists (SABA)			
Albuterol	ProAir HFA	October 29, 2004	Aerosol (inhalation)
	Proventil HFA	August 15, 1996	
	Ventolin HFA	April 19, 2001	
Fenoterol	Berotec	Not approved in the US	Aerosol (inhalation)
Levalbuterol	Xopenex	March 25, 1999	Solution (inhalation)
	Xopenex HFA	March 11, 2005	
Pirbuterol	Exirel	Could not identify	Powder (inhalation)
	Maxair	December 30, 1986	Aerosol (inhalation)
Terbutaline	Bricanyl	March 25, 1974	Aerosol (inhalation)
Anticholinergic drugs			
Ipratropium bromide	Atrovent HFA	November 17, 2004	Aerosol (inhalation)
Combination drugs			
Ipratropium bromide/ albuterol sulfate	Combivent	October 24, 1996	Aerosol (inhalation)

Note. Drugs in *red* are not indicated for asthma and are not of interest for this report presentation, but were included in the last report. Abbreviation. HFA: hydrofluoroalkane; SABA: short-acting beta agonist.

PICOS of Most Recent DERP Report (Quick Relief)

- *Outcomes*

- ❑ Symptoms (e.g., cough, wheezing, shortness of breath)
- ❑ Change in treatment regimen for the exacerbation
- ❑ Health care service use (e.g., length of stay, hospital admissions)
- ❑ Exercise tolerance, symptoms (for exercise-induced bronchospasm only)
- ❑ Mortality
- ❑ Adverse events (AEs; overall, serious AEs, and withdrawals due to AEs)

Key Questions in Most Recent DERP Report (Quick Relief)

- What is the comparative efficacy and effectiveness (KQ1) and harms (KQ2) of quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm?
- Are there any differences in effectiveness or harms between patient subgroups (KQ3)?

Summary of Findings in Most Recent DERP Report (Quick Relief)

- 2008 report
 - ▣ 10 trials (cumulative since original) comparing albuterol and levalbuterol for asthma; no studies identified for exercise-induced bronchospasm
 - 4 trials in adults, 5 trials in children
- Summary of key findings
 - ▣ Adult asthma (albuterol vs. levalbuterol)
 - Among adults, less rescue medication was required with levalbuterol (no between-group statistics), with no apparent difference in symptoms
 - In the emergency department (ED) setting, mixed results for hospitalization admission rates; some evidence for decreased admission with levalbuterol compared with albuterol in patients not using corticosteroids
 - For safety, no difference in withdrawals due to AEs and most specific AEs, although albuterol might result in greater increase in heart rate than levalbuterol
 - Results in studies including mostly African American adults were not stratified by race; no other studies stratified results by different populations of interest

Summary of Findings in Most Recent DERP Report (Quick Relief)

- Summary of key findings:
 - ▣ Asthma in children and adolescents (albuterol vs. levalbuterol)
 - In general, no difference in symptoms, rescue medications, or number of days of inadequate control, but may depend on dose
 - In the ED setting, no difference in symptoms and additional treatments required, but there may be some benefit for fewer hospital admissions with levalbuterol
 - Poor reporting of safety data across studies; in general, no difference in specific AEs, but there may be some evidence for higher rates of overall AEs with albuterol compared with levalbuterol
 - Results in studies including mostly African American children and adolescents were not stratified by race; no other studies stratified results by different populations of interest

Summary of Findings in Most Recent Surveillance (Quick Relief)

- Cumulative surveillance from most recent report through most recent 2015 scan (searched through December 2014)
 - No new drugs
 - No new boxed warnings or serious harms
 - No new comparative effectiveness systematic reviews
 - New head-to-head trials of albuterol versus levalbuterol
 - 2 in trials of pediatric populations

Note. List of new studies identified in scans/surveillance since last report attached

New FDA Drugs and Indications Since Last DERP Report (Quick Relief)

- **New drugs**

- 1 new fixed combination drug, 1 reapproved drug for over-the-counter (OTC) sale
 - Albuterol/budesonide (brand name [Airsupra](#))
 - Inhaled corticosteroid + short-acting beta-agonist, FDA-approved January 10, 2023
 - **Also of note:** epinephrine (brand name Primatene Mist, metered-dose inhaler) was [reapproved with new drug application](#) (NDA; with hydrofluoroalkane [HFA] propellant) in 2018 and is now the only FDA-approved OTC inhaler

- **New indications**

- Albuterol (ProAir HFA, Proventil HFA)
 - Expanded use to children at least 4 years (from 12 years) of age (September 2008)
 - *Already indicated for children at least 4 years for brand Ventolin HFA*

FDA-Approved Indications (Quick Relief)

- Indications as of January 24, 2024

Generic Name (Brand Name)	Treatment or Prevention of Bronchospasm in Patients with Reversible Obstructive Airway Disease	Prevention of Exercise-Induced Bronchospasm	Reduce Risk of Bronchospasm Exacerbations
Albuterol (ProAir HFA , Proventil HFA , Ventolin HFA)	✓ (≥ 4 years)	✓ (≥ 4 years)	
Albuterol/budesonide ^a (Airsupra)	✓ (≥ 18 years)		✓ (≥ 18 years)
Levalbuterol (Xopenex , Xopenex HFA)	✓ (≥ 6 years for Xopenex, ≥ 4 years for Xopenex HFA)		

Note. ^a Newly approved since last report.
Abbreviation. HFA: hydrofluoroalkane.

New FDA Warnings Since Last DERP Report and Pipeline Therapies (Quick Relief)

- **New warnings**

- No new boxed warnings or serious harms

- **Pipeline therapies**

- 1 new pipeline fixed-combination therapy
- TEV-56248 (albuterol/fluticasone propionate)
 - Inhaled corticosteroid + short-acting beta-agonist
 - Powder formulation (inhaled)
 - In phase 3 trials for the control of asthma symptoms

Generic Drug Status & Brand Discontinuations (Quick Relief)

Name	Generic Availability	Status
Albuterol (with HFA propellant)	Yes	<i>Newly available as generic since last report</i> <ul style="list-style-type: none">Some reports indicate that ProAir HFA brand has been recently discontinued
Albuterol/ budesonide ^a	No	Estimated loss of exclusivity, 2030
Levalbuterol	Yes	<i>Newly available as generic since last report</i>

Abbreviation. HFA: hydrofluoroalkane.

Clinical Practice Guidelines (Quick Relief; slide 1 of 5)

Overall asthma management

- Patient education and action plans are key
 - Learn skills to self-monitor for symptoms and control, appropriately use inhalers/medications, avoid environmental triggers
- Initiating pharmacotherapy
 - All patients with asthma should have immediate access to an inhaled bronchodilator (quick-relief agent)
 - Short-acting beta agonists (SABAs; albuterol or levalbuterol) is most common/traditional
 - For patients with moderate or severe asthma, or those with history of severe attacks, consider concomitant (or combination inhalers) low-dose glucocorticoid
 - Initial maintenance therapy is based on asthma severity, and adjustment of therapy is based on asthma control

Clinical Practice Guidelines (Quick Relief; slide 2 of 5)

- Maintenance therapy; step-care approach (steps 1 to 4+)
 - Adults and adolescents
 - Step 1 (intermittent and mild) – treatment as needed
 - **SABA** only (according to the National Asthma Education and Prevention Program [NAEPP] guidelines); low-dose inhaled corticosteroid (ICS)-**SABA** or low-dose ICS-formoterol (combined or as used together; according to the Global Initiative for Asthma [GINA] guidelines)
 - Step 2 (mild persistent) – treatment as needed
 - Low-dose ICS alone, or plus **SABA** (NAEPP); low-dose ICS-formoterol (GINA)
 - Leukotriene modifiers are alternatives when avoidance of ICS is necessary (lower efficacy)

Clinical Practice Guidelines (Quick Relief; slide 3 of 5)

- Maintenance therapy; step-care approach (steps 1 to 4+)
 - Adults and adolescents (cont.)
 - Step 3 (moderate persistent)
 - Low-dose ICS-formoterol preferred (both guidelines), and **SABA** or ICS-**SABA** as needed
 - Inhaled long-acting muscarinic antagonist (LAMA; tiotropium) can be equally effective as ICS-long-acting beta-2 agonist (LABA) and appropriate for any patient intolerant to formoterol/LABA
 - Step 4 (severe persistent)
 - Medium-dose ICS-formoterol preferred (both guidelines); other ICS-LABA treatments recommended as alternatives, with **SABA** as needed
 - Additional therapy with leukotriene modifiers, LAMAs, or biologic agents may be needed (consider new triple inhaler product for severe persistent asthma)
 - In rare situations, systemic glucocorticoids may be needed, but caution due to long-term effects; biologics may be newer option with fewer long-term AEs

Note. ^a Primary source [UpToDate](#); recommendations cross-referenced/verified against key clinical practice guidelines (slide 50). 20

Clinical Practice Guidelines (Quick Relief; slide 4 of 5)

- Maintenance therapy for children
 - Oral systemic corticosteroids are recommended if asthma attacks/exacerbations occur:
 - More than 2 days per week in children 2 to 3 years
 - Throughout the day in children > 3 to 12 years
 - Step-care approach
 - Step 1: **SABA** as needed; short course daily ICS and **SABA** as needed (> 4 years)
 - Step 2: Daily low dose ICS, and **SABA** as needed; daily low dose ICS (< 4 years)
 - Step 3: Daily and as need, low-dose ICS-formoterol; daily low-dose ICS-LABA or ICS plus leukotriene modifiers (< 4 years)
 - Step 4 and higher: Daily and as needed medium or high dose ICS-formoterol, or ICS-LABA (< 4 years) , and **SABA** as needed for serious cases; biologics considered for most severe cases

Clinical Practice Guidelines (Quick Relief; slide 5 of 5)

- Exercise-induced asthma (bronchoconstriction)
 - ▣ Exercise to improve cardiovascular fitness actually reduces risk for bronchoconstriction
 - ▣ This symptom in most patients with well-controlled asthma is often treated by:
 - Avoiding exercise in cold or dry air
 - Pharmacotherapy
 - **SABA** or combination ICS and formoterol pretreatment (5 to 20 minutes prior to activity)
 - **SABA** plus leukotriene modifiers or ICS for patients who require daily therapy for this symptom
 - ▣ If symptom persists, consider step-up treatment of underlying asthma condition

Key Clinical Practice Guidelines

Focus	Date	Title of Guideline
British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN)		
General asthma treatment	2019	British guideline on the management of asthma
Canadian Thoracic Society (CTS)		
General asthma treatment	2021	Diagnosis and management of asthma in preschoolers, children and adults
Global Initiative for Asthma (GINA)		
Management and prevention	2023	Global Strategy for Asthma Management and Prevention
National Asthma Education and Prevention Program (NAEPP) and National Heart, Lung, and Blood Institute (NHLBI)		
Update	2020	Focused Updates to the Asthma Management Guidelines
Diagnosis and management	2007	Guidelines for the Diagnosis and Management of Asthma
US Department of Veterans Affairs/Department of Defense (VA/DoD)		
Management in adults	2019	The Primary Care Management of Asthma

Questions?





**Adults & adolescents
12+ years**

Personalized asthma management

Assess, Adjust, Review
for individual patient needs

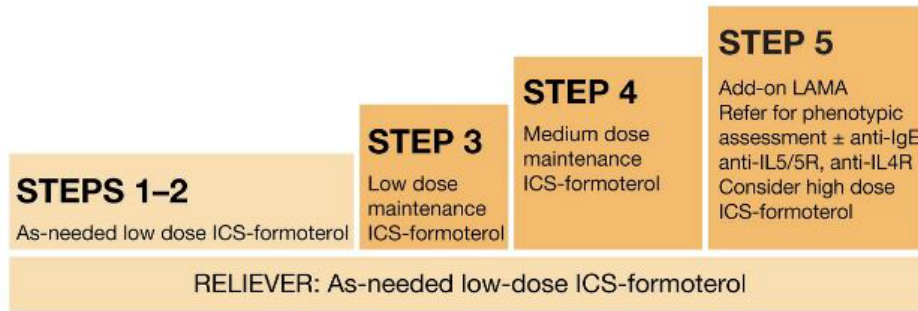
Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction



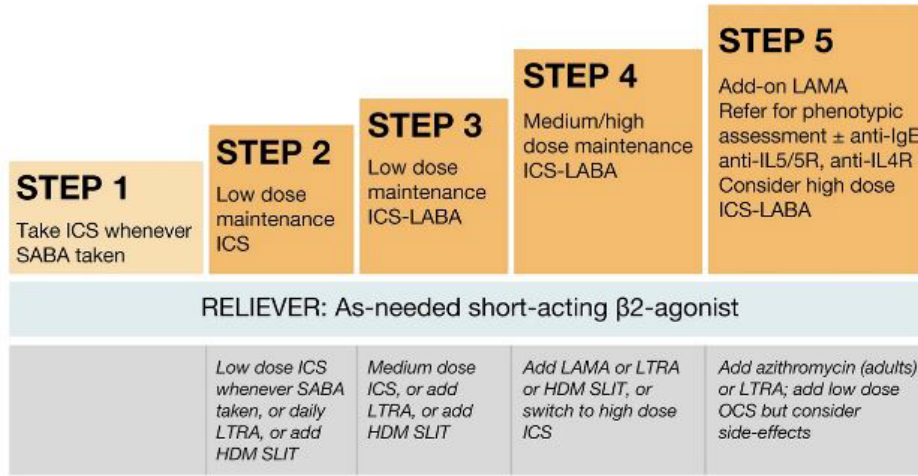
Confirmation of diagnosis if necessary
Symptom control & modifiable
risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

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



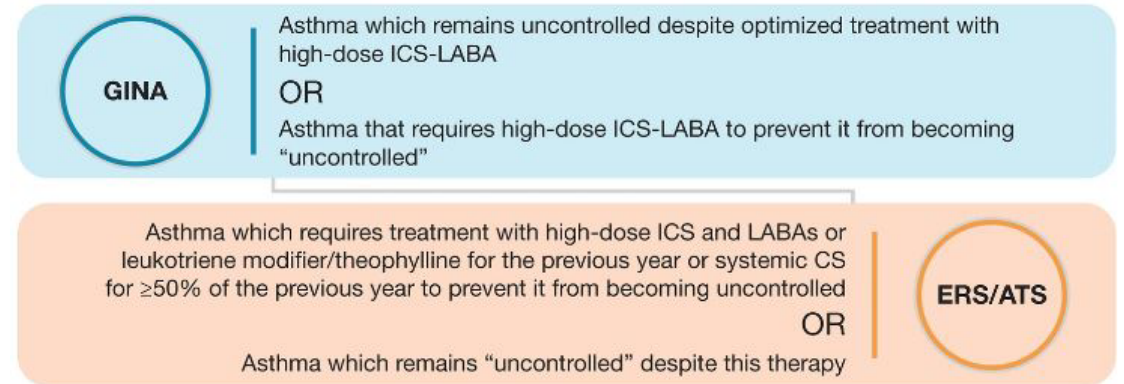
**CONTROLLER and
ALTERNATIVE RELIEVER**
(Track 2). Before considering a
regimen with SABA reliever,
check if the patients is likely to
be adherent with daily controller



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Source. [Calhoun et al., 2022](#)

Severe Asthma



a GINA recommended stepwise asthma treatment. **b** Severe asthma definition [1, 2]. ATS American Thoracic Society, BDP budesonide propionate, CS corticosteroids, ERS European Respiratory Society, FEV₁ forced expiratory volume in 1 s, GINA Global Initiative for Asthma, HDM house dust mite, ICS inhaled corticosteroids, IgE immunoglobulin E, IL interleukin, LABA long-acting β₂-agonist, LAMA long-acting muscarinic antagonist; LTRA leukotriene receptor antagonist, OCS oral corticosteroids; SABA short-acting β₂-agonist; SLIT sublingual immunotherapy