From inflammation to remission: Updates in adult asthma management

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Objectives

- Apply evidence-based management of mild asthma, with a focus on AIR and MART therapy
- Identify and differentiate difficult-to-treat asthma from severe asthma
- Understand role of biologics in the treatment of severe asthma, with a potential to achieve clinical remission

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Pediatric Objectives

- Recognize appropriate candidates for single maintenance and reliever therapy in a pediatric patient.
- Apply evidence-based medication management for intermittent asthma in a pediatric patient.
- Understand that there are multiple therapy options to treat pediatric asthma and therapy needs to be customized to the patient.

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Disclosures

- No financial disclosures

- The use of budesonide-formoterol on an as needed basis, and as single maintenance and reliever therapy (SMART) is **off-label use** in the US

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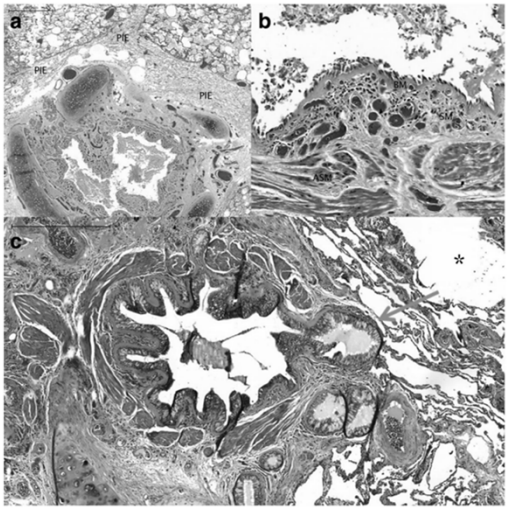
Asthma



"Heterogenous disease, usually characterized by chronic airway inflammation.

It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable airflow limitation.

One or more symptoms may predominate. Airflow limitation may later become persistent."

GINA 2024
Mauad et al. BMC Pulmonary Medicine 2018 https://doi.org/10.1186/s12890-018-0615-7

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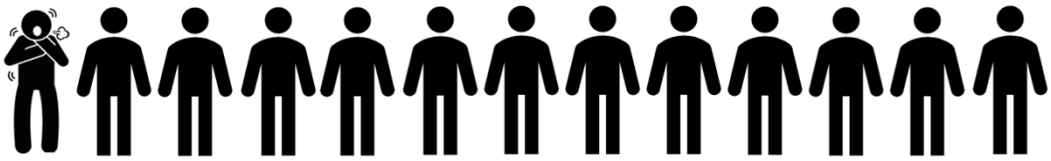
Asthma



1million ER visits

3,518 deaths

62% uncontrolled

30% misdiagnosed

>50% incorrect inhaler technique

cdc.gov- 2001-2021 data ; Aaron SD et al JAMA 2017 ; Melani AS et al Respir Med 2011; Souza ML J Bras Pneumol 2009

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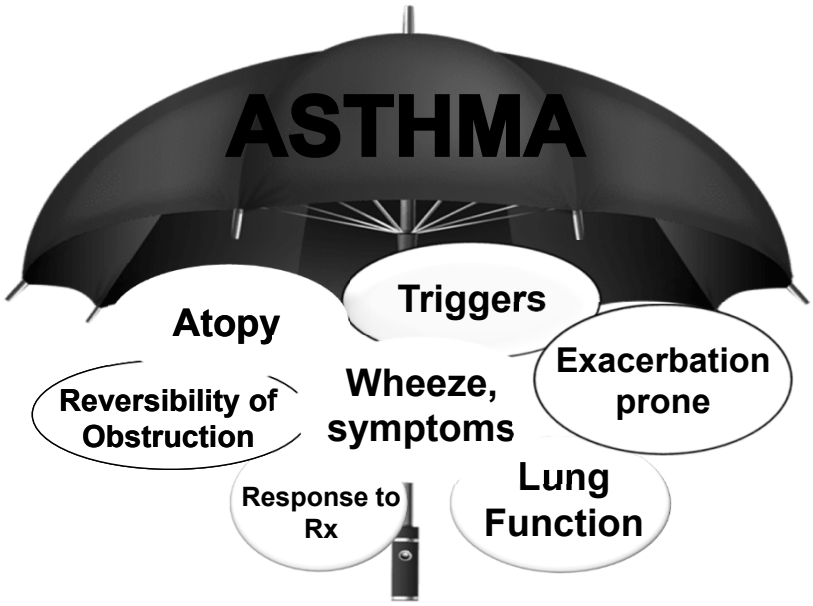
Early Onset



Late Onset

Phenotype: Observable properties

Newby C. PLoS One 2014
Nair P Clin Chest Med. 2012

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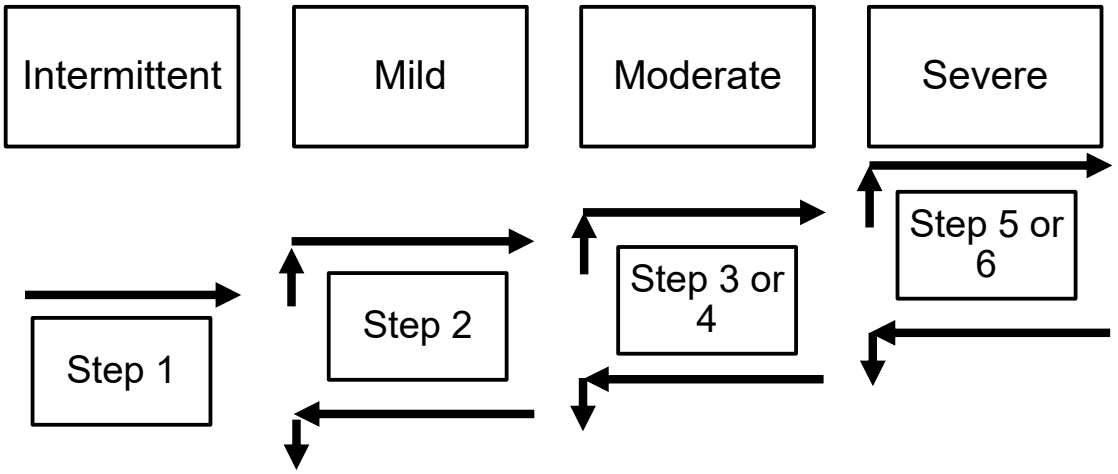
Definitions- asthma severity



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Definitions- treatment class

- ICS: Inhaled Corticosteroid
  - Budesonide, mometasone, fluticasone, beclomethasone etc
- LABA: Long-Acting Beta Agonist
  - Formoterol, salmeterol, vilanterol as ICS- combination therapy
- SABA: Short-Acting Beta Agonist
  - Albuterol, levalbuterol
- LAMA: Long-Acting Muscarinic Antagonists
  - Tiotropium, umeclidium, glycopyrrolate etc

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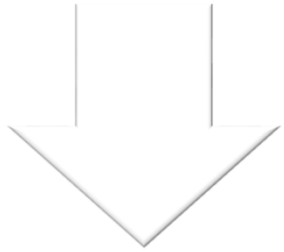
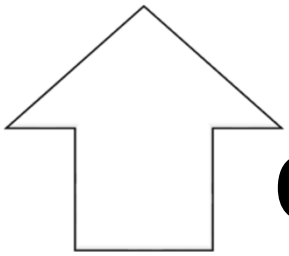
Treatment Goals in Asthma

risk





control

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Definitions- treatment concepts

- **(S)MART**: **s**ingle **M**aintenance and **R**eliever **T**herapy
  - Most data in budesonide-formoterol
  - "ICS-**formoterol"**
  - Not just a *single* inhaler- need 2! *(home and school/work)*

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- **AIR**: **A**nti-**i**nflammatory **R**eliever
  - Inhaled corticosteroid- **formoterol**
  - Budesonide- albuterol
  - AIR- only, ICS LABA with AIR therapy, MART provides AIR

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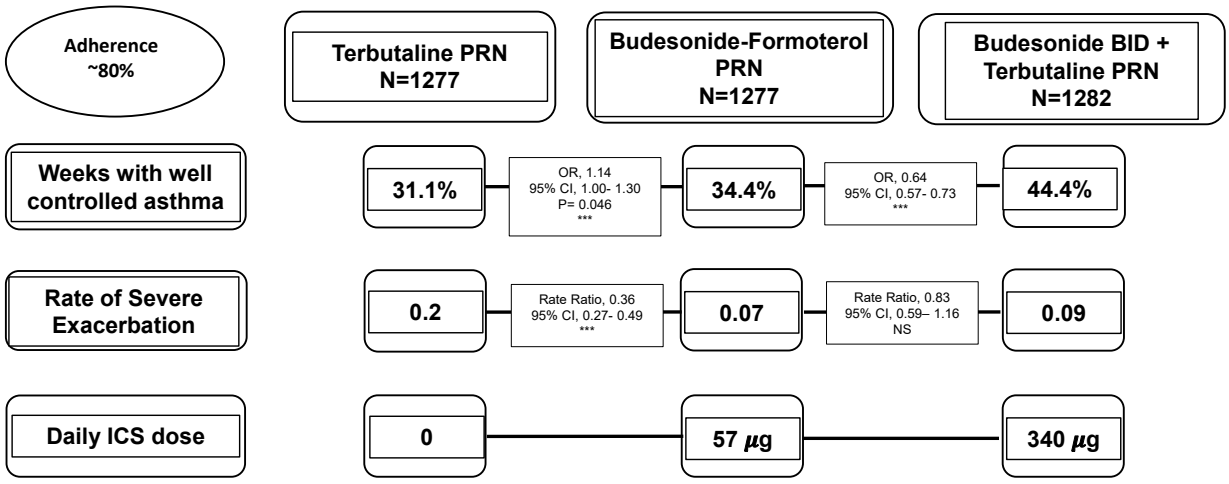
Symbicort Given As Needed in Mild Asthma 1

Mild asthma: SABA vs ICS-LABA PRN vs ICS BID



O'Byrne et al NEJM 2018

SYGMA 2 Bateman et al NEJM 2018
NOVEL START Beasley et al NEJM 2019
PRACTICAL Hardy J et al Lancet 2019

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ICS- formoterol provides superior exacerbation reduction across asthma spectrum

Table1. Risk of severe asthma exacerbations with ICS/formoterol reliever vs SABA reliever according to maintenance treatment

ICS/formoterol alone vs SABA alone[14]	OR, 0.45; 95% CI, 0.34- 0.60
ICS/formoterol alone vs low-dose ICS plus SABA[14]	OR, 0.79; 95% CI, 0.59- 1.07
ICS/formoterol SMART vs same-dose ICS plus SABA[13]	RR, 0.64; 95% CI, 0.53- 0.78
ICS/formoterol SMART vs 2× dose ICS plus SABA[13]	RR, 0.59; 95% CI, 0.49- 0.71
ICS/formoterol SMART vs same-dose ICS/LABA plus SABA[13]	RR, 0.68; 95% CI, 0.58- 0.80
ICS/formoterol SMART vs 2× dose ICS/LABA plus SABA[13]	RR, 0.77; 95% CI, 0.60- 0.98

OR, Odds ratio; *RR*, risk ratio.

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Anti-Inflammatory Reliever Therapy

- Deliver reliever with ICS
  - Treat symptoms and inflammatory etiology
- How to dose AIR:
  - Budesonide- Formoterol 160/4.5 mcg 1 puff PRN
  - Budesonide- Formoterol 80/4.5 mcg 2 puff PRN
  - As of 2024: Budesonide- Albuterol 80/90 2 puff PRN
  - *Max daily: 12 inhalations*

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What about ICS-Albuterol?

- 12 + with uncontrolled moderate to severe asthma on scheduled ICS +/- LABA
- Budesonide-Albuterol 160/180 PRN reduced risk of severe exacerbation compared to albuterol 180 alone *(n= 3,123)*
- Both albuterol and budesonide components contribute efficacy in improved lung function
- Ongoing trial using BUD-ALB as step 1 therapy

MANDALA Papi A NEJM 2022 | DENALI Chipps B CHEST 2023 | BATURA design LaForce C J Asthma Allergy 2024

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Budesonide- albuterol labelling

- As needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients ≥18 years of age with asthma.

- AIR added to maintenance ICS therapy

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Guiding Publications

GLOBAL INITIATIVE FOR ASTHMA

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

NIH/NAEPP Expert Panel Report

Ginasthma.org
Nhlbi.nih.gov/AsthmaGuidelines

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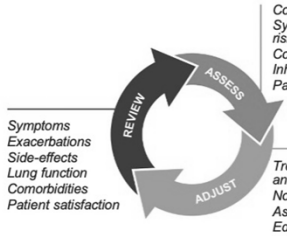
GINA 2024 – Adults & adolescents 12+ years

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



TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only 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-IL4Rα, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol*			

See GINA severe asthma guide

TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

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-IL4Rα, anti-TSLP
RELIEVER: As-needed ICS-SABA*, or as-needed SABA				

Other controller options (limited indications, or less evidence for efficacy or safety – see text)			
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 add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

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AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 ■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

Nhlbi.nih.gov/AsthmaGuidelines
Cloutier MM et al JACI 2020

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SABA only therapy in adults: out of favor

- Adverse effects and clinical outcomes
- Even mild asthma at risk for severe exacerbation and fatal events
- Disease of ~~bronchoconstriction~~ Inflammation
  - Patient conceptualized primary treatment matters
- Pragmatic consideration: adherence to scheduled Rx

Dusser Allergy 2007 | Suissa S et al Am J Respir Crit Care Med 1994 | Aldridge RE et al Am J Respir Crit Care Med 2000 | Hancox RJ et al Respir Med 2000

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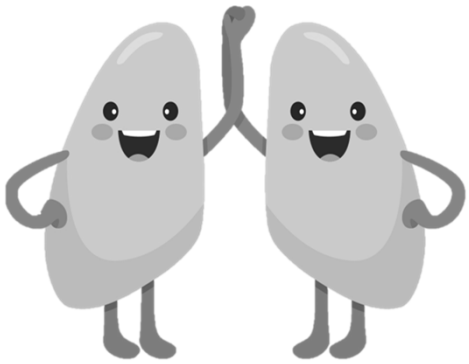
- Titration of ICS to symptoms more effective at preventing exacerbations
- Anti-inflammatory reliever across all steps of asthma therapy:
  - ICS-formoterol MART or
  - ICS-SABA
- Paradigmatic change



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