A Practice Change is Coming: review of the 2019 Global Initiative for Asthma report

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Disclosures

- I have nothing to disclose
- I will be discussing off-labeled use of medication (EVERYDAY)

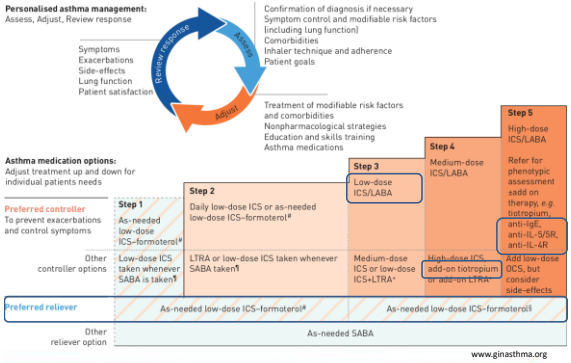
Objectives

1. Discuss the preferred controller therapies for asthma treatment
2. Compare low-dose inhaled corticosteroid / formoterol to short-acting beta2-agonist reliever therapy for acute asthma

Asthma Guides

NAEPP EPR3 2007 → GINA 2019 → NAEPP EPR4 in development

US Department of Health and Human Services. Publication No. 07–4051; 2007, www.ginasthma.org, www.nhlbi.nih.gov/about/advisory-and-peer-review-committees/national-asthma-education-and-prevention-program-coordinating/EPR4-working-group



Pharmacologic Therapy

- **Long term control**
  - Anti-inflammatory
    - Inhaled corticosteroids (ICS)
    - Mast cell stabilizers
    - Leukotriene modifiers
    - **Biologics**
  - Bronchodilators
    - **Long-acting β2-agonists (LABA)**
    - **Long-acting muscarinic antagonists (LAMA)**
    - Theophylline
- Quick relief
  - Short-acting β2-agonists (SABA)
  - Systemic corticosteroids
  - Short-acting anticholinergic agents

Long-acting β_2-agonists

WARNING

Long-acting beta$_2$-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo when added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

- FDA removed box warning in late 2017 after several safety trials found no significant increase in serious asthma outcomes

Step-Up in Asthma Therapy

+ LABA (as needed)	• **Preferred strategy** • Lower dose ICS needed for control • Fewer severe exacerbations, less HS symptoms, improve QOL
Increase ICS	• Quadrupling has better effect than doubling • Increased risk of systemic adverse effects
+ LAMA	• Noninferiority to LABA
+ LABA / LAMA	• May reduce exacerbations

Ann Allergy Asthma Immunol 2017;118:133-142, Ann Allergy Asthma Immunol 2018;120:559-579

Long-acting Muscarinic Antagonist Meta-analysis

Purpose
- Evaluate effects associated with LAMA vs placebo or vs other controllers as an add-on therapy to ICS and to ICS / LABA in uncontrolled, persistent asthma

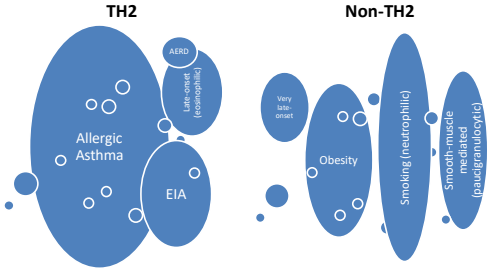
Methods
- MEDLINE, Embase, and Cochrane Databases and Clinical Trials registries through November 2017

Results
- 15 randomized trials, n=7122
- **adding LAMA vs placebo to ICS**: RR 0.67 (95% CI, 0.48-0.92)
- **- adding LAMA vs LABA to ICS**: RR 0.87 (95% CI, 0.53-1.42)
- **triple therapy vs ICS / LABA**: RR 0.84 (95% CI, 0.57-1.22)

Conclusion
- Use of LAMA compared with placebo as add-on therapy to ICS is associated with lower risk of exacerbation

JAMA 2018;319:1473-1484

Asthma Phenotypes



Nature Medicine 2012;18:716-725

Available Biologics

Drug	Target	Age	Route	Indication	Adverse Effects
Omalizumab (Xolair)	IgE	6	SQ	-Sensitization on skin prick testing or specific IgE, increase total serum IgE -Idiopathic urticaria	headache, eosinophilia/vasculitis, arthralgia, malignancy
Mepolizumab (Nucala)	IL-5	6	SQ*	-Blood eosinophils ≥300/µl -Nasal polyps	herpes zoster infection
Benralizumab (Fasenra)		12	SQ*		
Reslizumab (Cinqair)		18	IV		malignancy
Dupilumab (Dupixent)	IL-4 (and IL-13)	12	SQ*	-Blood eosinophils ≥150/µl or FeNO ≥25ppb -Nasal polyps -Atopic dermatitis	eosinophilia/vasculitis, ocular effects

*Available in prefilled syringe for possible home use

Steroids in Eosinophil Negative Asthma (SIENA) Trial

Purpose
- Compare an inhaled corticosteroid and tiotropium with placebo in mild, persistent asthma, according to the patients' sputum eosinophil level at baseline

Methods
- RDBPC, crossover trial, 42-weeks
- n=295, >12 years with mild, persistent asthma and categorized by <2% or ≥2% sputum eosinophils
- Mometasone Twisthaler 220 mcg or HFA 200 mcg BID, tiotropium Respimat 5mcg daily, placebo

Results
- 73% had low eosinophils
- **Mometasone**: 57% (95%CI, 48-66) had a better response vs 43% (95% CI 34-52) to placebo (P=0.14)
- **Tiotropium**: 60% (95%CI, 51-68) had a better response vs 40% (95% CI, 32-49) to placebo (P=0.029)

Conclusion
- A majority of patients with mild, persistent asthma had low sputum eosinophils and had no significant difference in response to either mometasone or tiotropium compared to placebo

N Engl J Med 2019;380:2009-19

Patient Case 1

- TG is an 12-year-old on Step 3 therapy with fluticasone/salmeterol HFA 45/21 mcg 2 puffs BID and poorly controlled symptoms and frequent exacerbations. She also has allergic rhinitis, food allergies, and eczema.
- What is the most appropriate step-up therapy for TG's asthma?
  a. Increase fluticasone/salmeterol 115/21 mcg, 2 puffs BID
  b. Add tiotropium Respimat 1.25 mcg, 2 puffs daily
  c. Add montelukast 5mg PO HS
  d. Refer for possible biologic therapy

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  - **Inhaled corticosteroids (ICS) + formoterol**
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Single Inhaler Therapy (SIT) or Single Maintenance and Reliever Therapy (SMART)

Formoterol

Mechanism	selective β_2-agonist
Pharmaco-kinetics	• Onset 5-15 min • Duration 12 hours
Reliver Dose	• Budesonide 80 or 160 mcg / formoterol 4.5 mcg: 1 puff as needed • Seek medical attention if using > 12 puffs/day • Mometasone / formoterol: unknown
Clinical Pearls	**Avoid using other LABA for reliever**

www.ginasthma.org, Symbicort package insert 2017

ICS / Formoterol Evidence

Study	Design	Sample	Intervention	Outcomes
SYGMA-1	RDBPC, 52 weeks	n=3849, ≥12 years, mild asthma	Budesonide/ formoterol Turbuhaler 200/6 mcg prn vs terbutaline prn or vs budesonide 200 mcg BID + terbutaline prn	-Asthma control: OR 1.14, 95%CI 1.00-1.30 and 0.64, 95%CI 0.57-0.73 -Severe exacerbation: RR 0.36, 95%CI 0..27-0.49 and 0.83, 95%CI 0.59-1.16 -More AE with terbutaline
SYGMA-2	RDBPC, 52 weeks	n=4215, ≥12 years, mild asthma	Budesonide/ formoterol Turbuhaler 200/6 mcg prn vs budesonide 200 mcg BID + terbutaline prn	-Annualized rate of severe asthma exacerbations: 0.11, 95%CI 0.01-0.13 vs 0.12, 95%CI 0.10-0.14 -Improved symptom control with maintenance

N Engl J Med 2018;378:1865-76, N Engl J Med 2018;378:1877-87

ICS / Formoterol Evidence

Study	Design	Sample	Intervention	Outcomes
Novel START	Open-label RCT, 52 weeks	n=668, ≥18 years, mild asthma	Budesonide/ formoterol Turbuhaler 200/6 mcg prn vs albuterol prn or vs budesonide 200 mcg BID + albuterol prn	Annualized rate of severe asthma exacerbations: 0.195 vs 0.4 and 0.195 vs 0.175
PRACTICAL	Open-label RCT, 52 weeks	n=890, ≥18 years, mild-moderate asthma	Budesonide/ formoterol Turbuhaler 200/6 mcg prn vs budesonide 200 mcg BID + terbutaline prn	Annualized rate of severe asthma exacerbations: 0.119 vs 0.172

N Engl J Med 2019;380:2020-30, Lancet 2019;394:919–28

Single Maintenance and Reliver Therapy Meta-analysis

Purpose
- Evaluate SMART in persistent asthma

Methods
- MEDLINE, Embase, and Cochrane Databases and Clinical Trials registries through November 2017

Results
- 16 randomized trials, n=22,524 patients ≥12 years, n=341 patients 4-11 years
- **SMART vs same dose ICS:** RR 0.64 (95%CI, 0.53-0.78)
- **SMART vs same dose ICS / LABA**: RR 0.68 (95%CI, 0.58-0.80)
- **SMART vs higher dose ICS / LABA**: RR 0.77 (95%CI, 0.60-0.98)

Conclusion
- Use of SMART lowers risk if asthma exacerbation, evidence for 4-11 years is limited

JAMA 2018;319:1485-1496

ICS / Formoterol Discussion

Pros
- Overcome misconception regarding disease and SABA
- Improve adherence ICS
- Less ICS exposure

Cons
- Formulation studied unavailable in US
- Not approved in US
- Payor may measure nonadherence
- History of frequent exacerbation still require action plan with SABA

Patient Case 2

- TJ is a 15-year-old female who has been coughing a few times per month. She was using an albuterol inhaler that she received for a respiratory infection last winter, but recently ran out of the medication. Her sleep and activities are not limited by her symptoms. Her FEV1 is 82% predicted.
- Which regimen is best for managing TJ's asthma?
  a. Continue albuterol per action plan
  b. Initiate budesonide/formoterol 80/4.5 mcg, 1 puff as needed
  c. Initiate budesonise/formoterol 80/4.5 mcg, 2 puffs BID and 1 puff as needed
  d. Initiate fluticasone 44 mcg, 2 puffs BID and albuterol per action plan

Summary

- LABAs are preferred in combination with ICS for asthma control
- Tiotropium and asthma biologics are additional controller options
- Practical considerations need to be addressed as reliever therapy shifts to ICS / Formoterol as needed

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