Modern Asthma Care:
Towards a "SMART" and Personalized Approach

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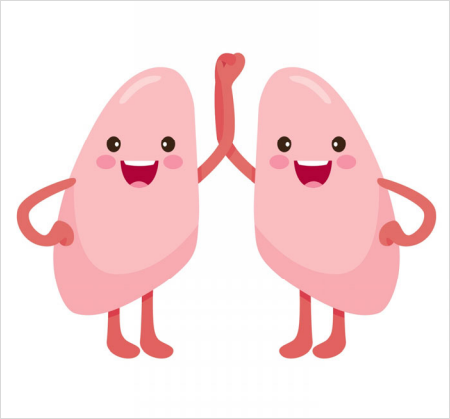
Disclosures

No conflicts of interest to disclose

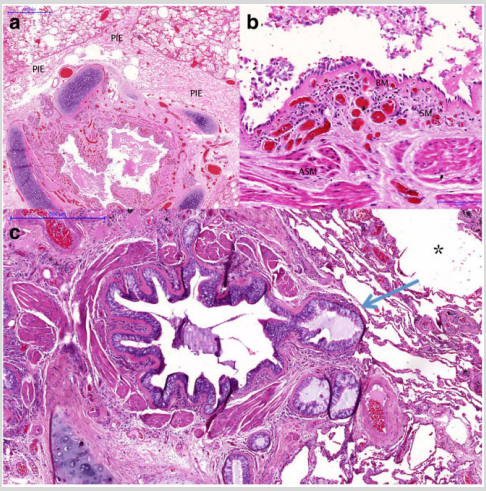
The use of budesonide-formoterol on an as needed basis, and as single maintenance and reliever therapy (SMART) is **off-label use** in the US

Objectives



- Describe outcomes in asthma patients with COVID- 19
- Apply updated evidence and guideline recommendations in the management of mild asthma, with a focus on SMART therapy
- Identify and differentiate difficult-to-treat asthma from severe asthma
- Understand the significance of asthma phenotypes and the role of biologic therapies in the treatment of severe asthma

Asthma



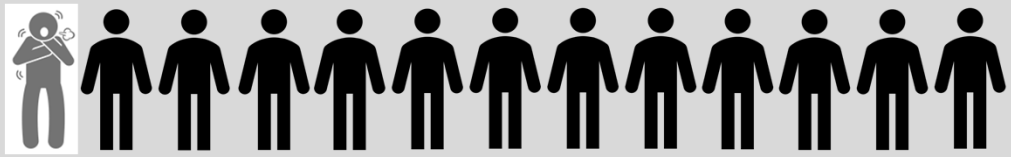
"Heterogenous disease, usually characterized by chronic airway inflammation.

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"

GINA 2020
Mauad et al. BMC Pulmonary Medicine 2018 https://doi.org/10.1186/s12890-018-0615-7

Asthma

by the numbers



1.5 million ER visits

3,518 deaths

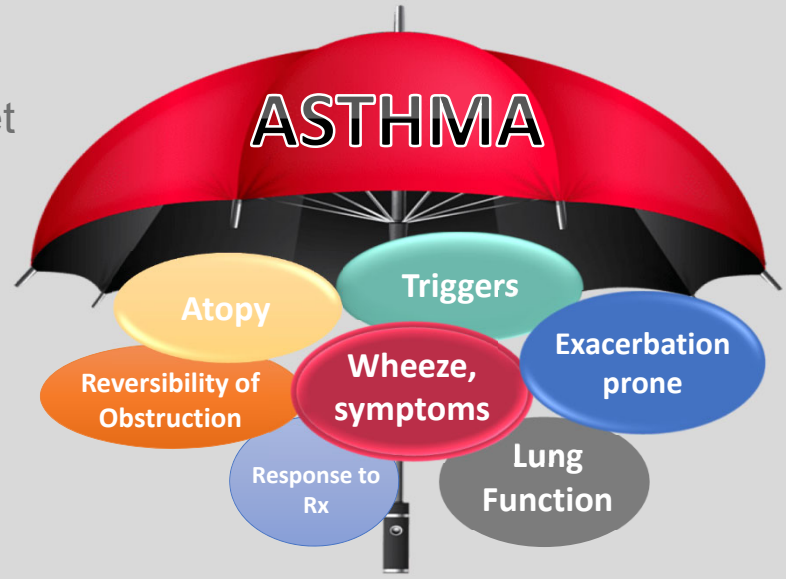
62% uncontrolled

30% misdiagnosed

>50% incorrect inhaler technique

cdc.gov- 2018 data
Aaron SD et al JAMA 2017
Melani AS et al Respir Med 2011
Souza ML J Bras Pneumol 2009

Early Onset



Late Onset

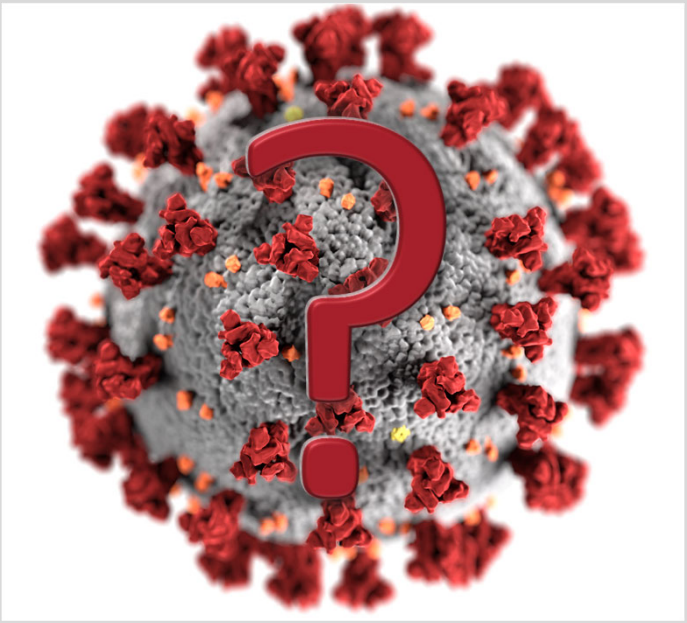
Phenotype: Observable properties

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

Modern Asthma Care

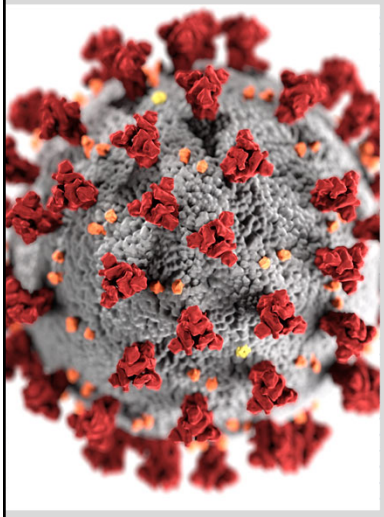
Towards a SMART and Personalized Approach

But first…



Asthma and COVID-19

Viral infections are the #1 cause of asthma exacerbations



Rhinovirus
>80%

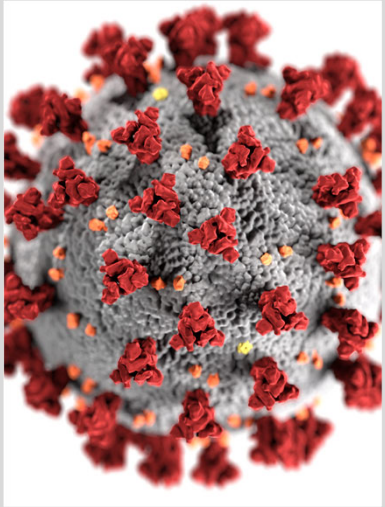
Influenza
~15%

Enterovirus
Adenovirus
RSV
Coronavirus
<5%

Grissell TV et al *Am J Respir Crit Care Med* 2005
Wark PA Gibson PG *Thorax* 2006

Asthma and COVID-19

Hypothesis: protective from infection?

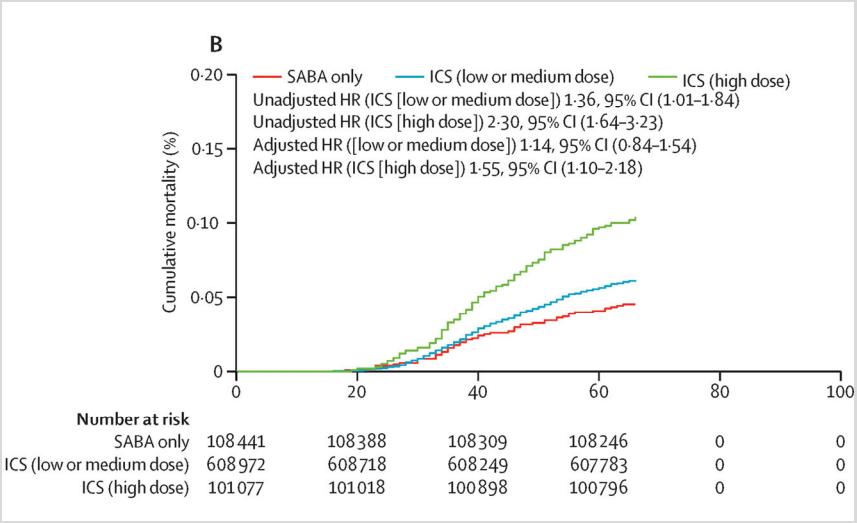


- SARSCoV2 utilizes ACE2 and TMPRSS2 receptors for cell entry
- Inhaled corticosteroid (ICS) use down-regulates expression of ACE2 and TMPRSS2
- ACE2 expression is decreased in allergic sensitization
- T2 high inflammation reduces ACE2 gene expression

Peters, et al. Am J Respir Crit Care Med. 2020
Jackson DJ et al J Allergy Clin Immunol 2020
Camiolo et al J Allergy Clin Immunol 2020

Asthma and COVID-19

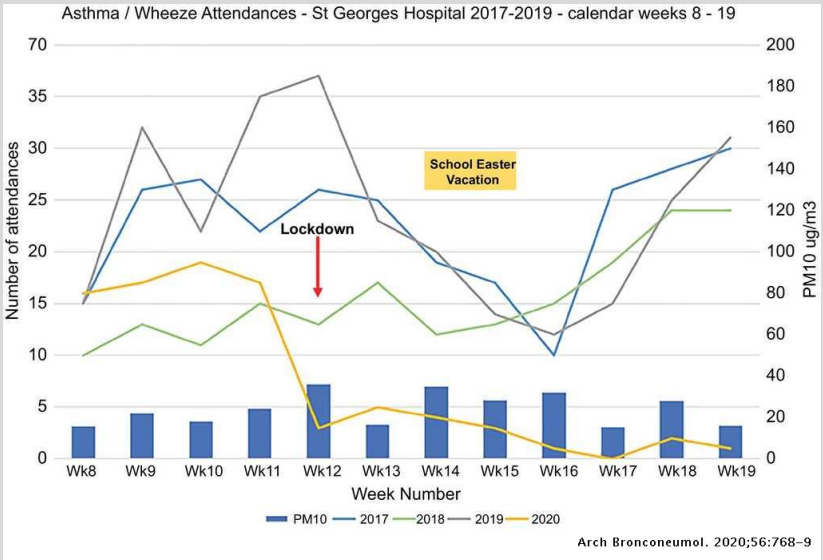
Clinical Experience: ICS and outcomes



Schultze A et al Lancet Respir Med 2020

Asthma and COVID-19

Pediatric ER visits - London

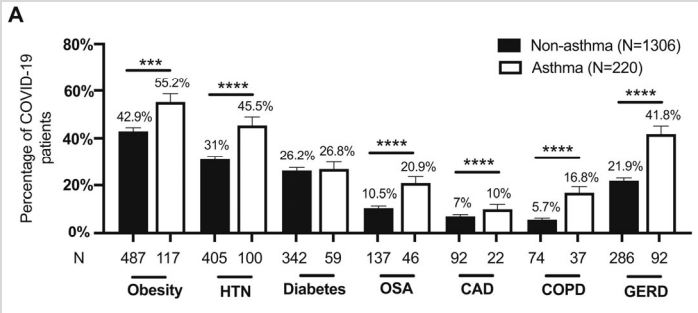


Chavasse R et al Arch Bronconeumol 2020
Abe K et al J Allergy Clin Immunol Pract 2020

Asthma and COVID-19

At increased risk for severe disease?

- In the US: asthma prevalence is 7.4% - 17% in COVID-19 hospitalized patients
  - Asthma prevalence in the US is 7.7% (2018)
- Chicago: Asthma conferred no increased risk for hospitalization or mortality



Chhiba KD et al J Allergy Clin Immunol 2020
www.cdc.gov – 2018 data

Asthma and COVID-19

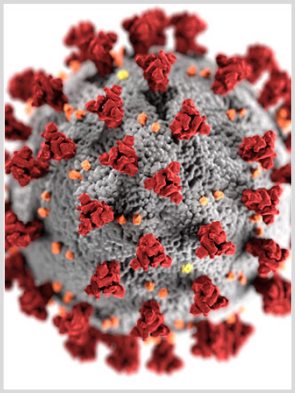
Asthma + severe COVID-19 has no worse outcome- NYC surge

	No Asthma (N= 1135)	Asthma (N= 163)	P- value
Length of Stay, Median (IQR)	5 (7)	6 (9)	0.25
Readmission	55 (5%)	9 (5%)	0.70
Intubations	231 (20%)	34 (21%)	0.92
Tracheostomy	71 (6%)	10 (6%)	1.00
Death	101 (9%)	9 (6%)	0.18

Lovinsky-Desir S et al J Allergy Clin Immunol 2020

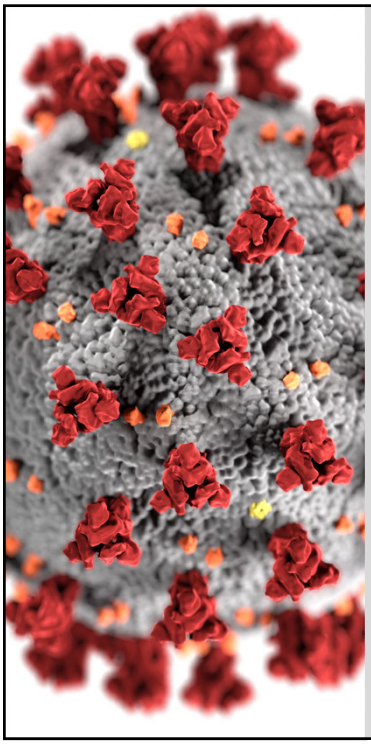
Asthma and COVID-19

High risk?



At increased risk for severe illness	Might be an increased risk for severe illness
COPD	**Moderate-to-severe asthma**
Smoking	Cystic fibrosis
Solid Organ Transplant	Pulmonary fibrosis
Obesity (BMI >30 to <40) & Severe Obesity BMI >40	Obesity (BMI >25 but <30)
Pregnancy	Hypertension
Sickle Cell Disease	Immunocompromise (not solid organ)
Down Syndrome	Liver Disease
Cancer	Thalassemia
Chronic Kidney Disease	Hypertension
Heart Disease (CHF, CAD, CM)	Neurologic conditions; cerebrovascular dz
Type 2 Diabetes	Type 1 Diabetes

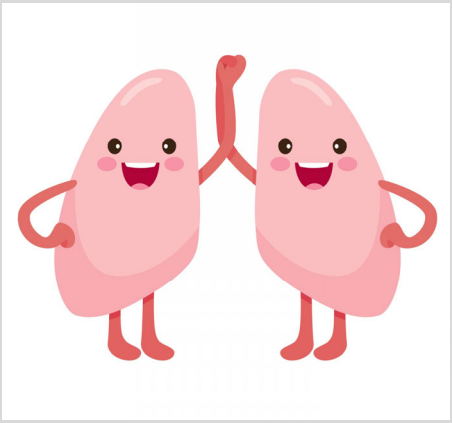
www.cdc.gov updated December 23, 2020



Summary
Asthma and COVID-19

- Asthma may place one at increased risk for more severe COVID
- However, there is pathophysiologic hypothesis for potential protection from infection, and data appears reassuring that asthmatics are not disproportionately ill
- The best way to prevent asthma flare is with better asthma control; adherence to controller medications remains important in the pandemic
  - OR are masking & staying home even better?

Objectives



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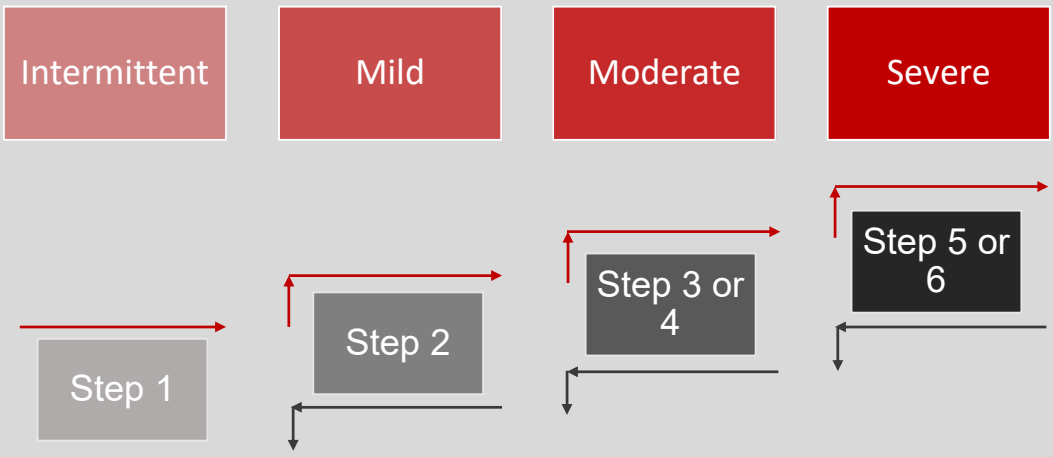
Asthma Severity

Classified by treatment required to maintain control



Treatment of asthma

risk

control

Treatment of asthma

risk

control

Treatment of asthma

risk

control

Mild Asthma

'silent' majority?

- 50- 75% of asthmatics
  - At risk for severe exacerbations & fatal events
  - 30% of ER admissions for acute asthma
- Short Acting Beta Agonist therapy (SABA)
  - Disease of bronchoconstriction

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

Mild Asthma

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- 50- 75% of asthmatics
  - At risk for severe exacerbations & fatal events
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- Short Acting Beta Agonist therapy (SABA)
  - Disease of ~~bronchoconstriction~~ Inflammation
  - SABA-only: adverse effects & adverse clinical outcomes

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

Inhaled corticosteroids (ICS) in mild asthma

ICS reduces risk, even used PRN

- ICS substantially reduces risk of hospitalizations, severe exacerbations & asthma-related death
- Even among those with symptoms 0-1 day/week
- GINA 2014: daily ICS if symptoms 2x/month

Reddel HK et al Lancet 2017
Papi et al NEJM 2007

Single Maintenance and Reliever Therapy

aka SMART

- Formoterol: Quick onset, long acting beta agonist
- 16 RCTs: ICS-Formoterol SMART reduces risk of exacerbation compared to ICS alone, same, or higher dose ICS-LABA
- Improvement in control is more elusive

Sobieraj DM et al JAMA 2018

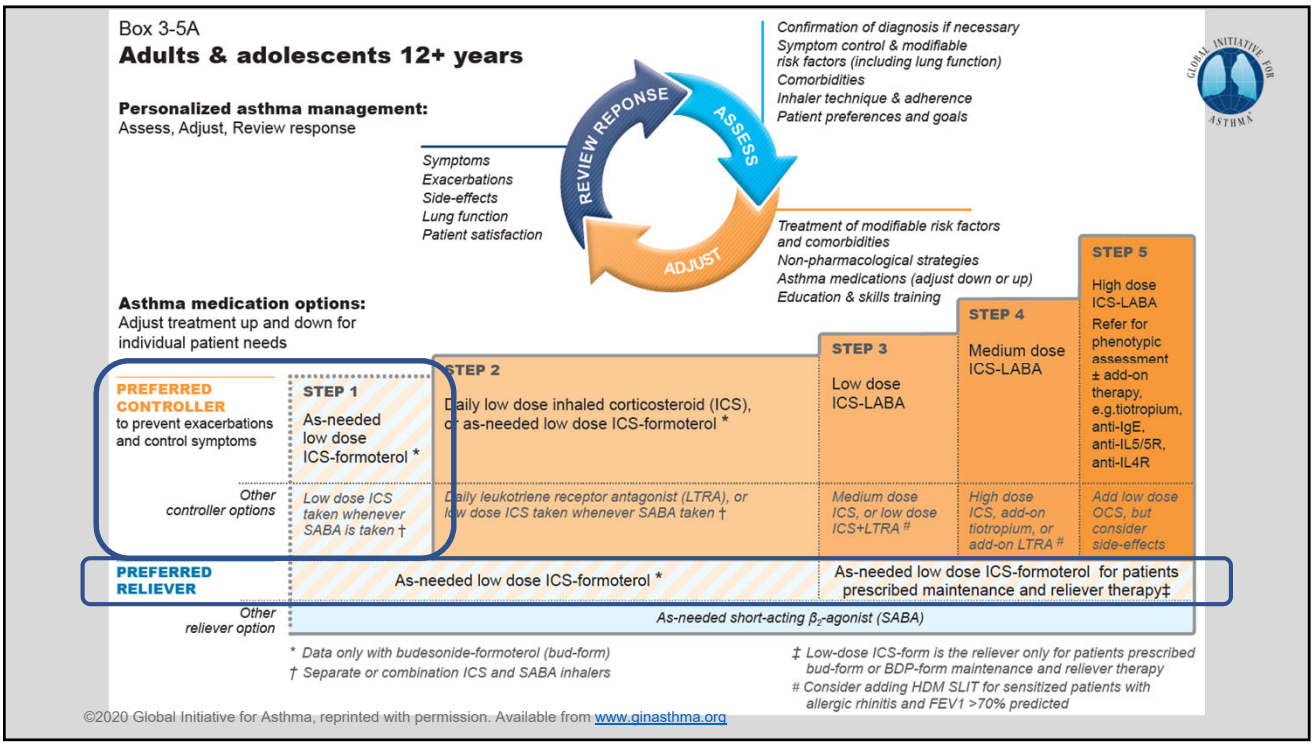
Guiding Publications

GINA & NIH/NAEPP Expert Panel Report

GLOBAL INITIATIVE
FOR ASTHMA

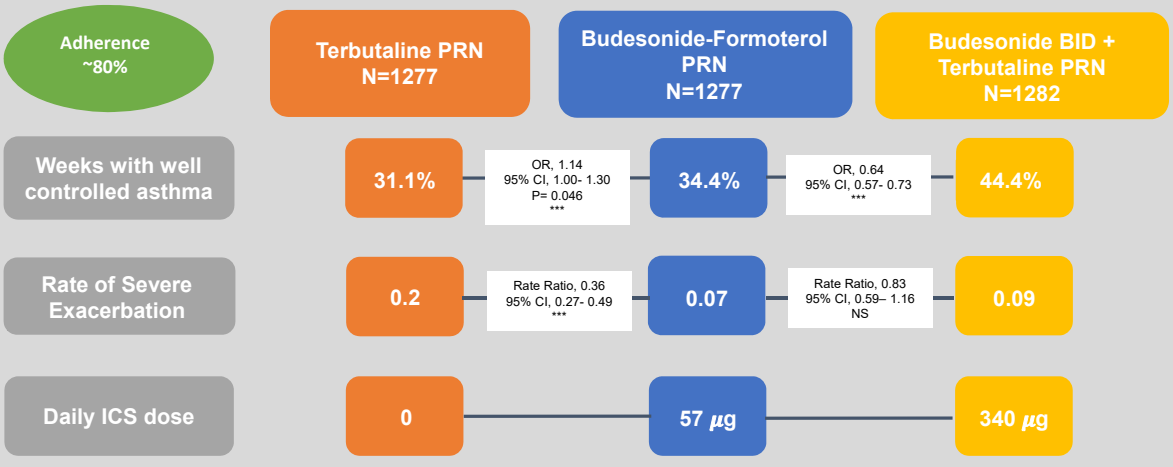
U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

Ginasthma.org
Nhlbi.nih.gov/AsthmaGuidelines



Symbicort Given As Needed in Mild Asthma 1

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



O'Byrne et al NEJM 2018

Symbicort Given As Needed in Mild Asthma 1

ICS-formoterol PRN superior vs SABA, non-inferior ICS BID

Terbutaline PRN N=1277	Budesonide-Formoterol PRN N=1277	Budesonide BID + Terbutaline PRN N=1282

In mild asthma **PRN ICS-LABA** is superior to **PRN SABA** with regards to both asthma control and reduction of risk of exacerbation.

O'Byrne et al NEJM 2018

Symbicort Given As Needed in Mild Asthma 2

ICS-formoterol PRN is non-inferior to ICS

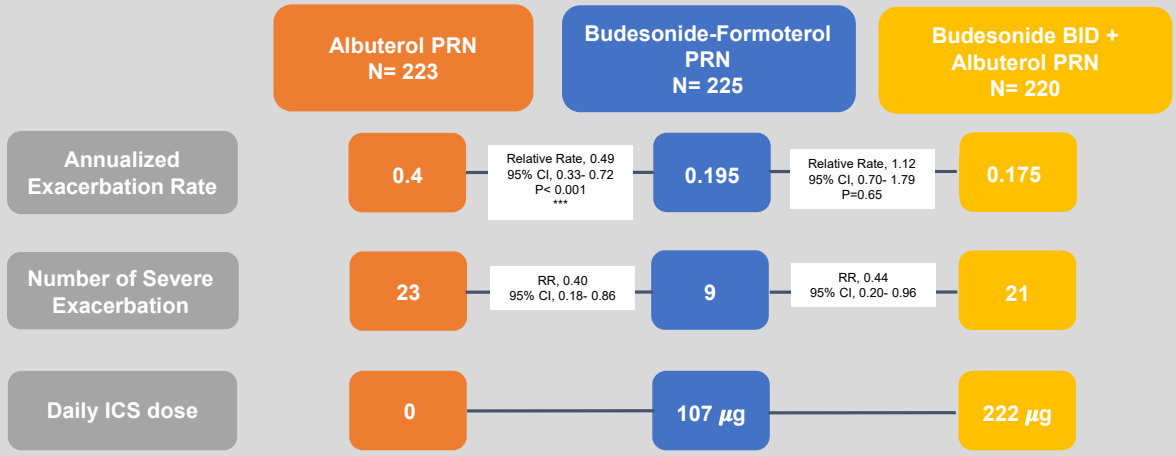
Adherence ~63%

	Budesonide-Formoterol PRN N=2084		Budesonide BID + Terbutaline PRN N=2083
Annualized Exacerbation Rate	0.11	Rate Ratio, 0.97 95% CI UL 1.16 P= 0.003 ***	0.12
Change in FEV1 pre- bronchodilator	104 mL	Δ -32.6 mL (95% CI, -53.7 to -11.4) P= <0.001 ***	136.6
Δ ACQ-5 Score from baseline	-0.35	Δ 0.11 (95% CI, 0.07- 0.15) P<0.001 ***	-0.46
Daily ICS dose	66 µg		267 µg

Bateman et al NEJM 2018

Novel START

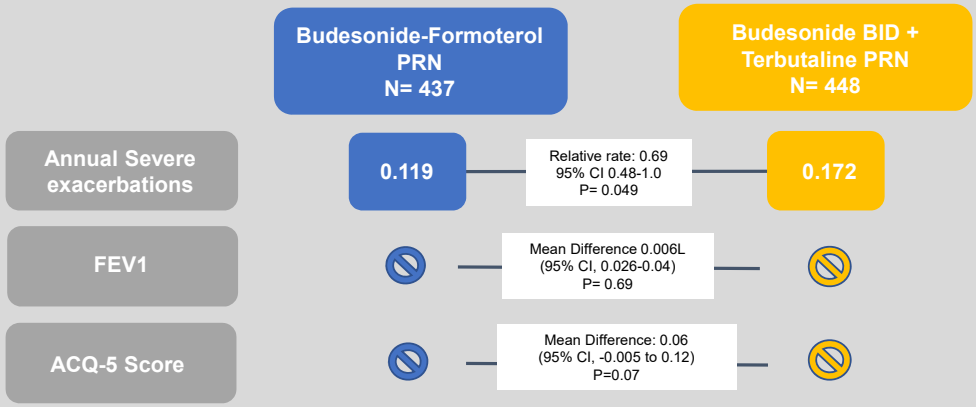
ICS-formoterol PRN is superior to SABA PRN



Beasley et al NEJM 2019

PRACTICAL trial

ICS-formoterol PRN fewer mod-severe exacerbations vs ICS



Hardy J et al Lancet 2019

NIH- NAEPP Focused Update

December 2020

areas of focus

- Intermittent inhaled corticosteroids
- Add on long-acting muscarinic antagonists
- Fractional exhaled nitric oxide
- Indoor allergen mitigation
- Immunotherapy
- Bronchial thermoplasty

Cloutier MM JAMA 2020

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

Black Box Warning

ICS-LABA does not increase the risk of asthma-related death. FDA removed black box warning in 2018. It is not recommended to use LABA alone in asthma

March 2020 FDA added a black box warning to montelukast (Singulair) for neuropsychiatric effects
Suggests against use for uncomplicated allergic rhinitis alone

Summary
Asthma Guidelines

- Exposure to inhaled corticosteroids is key in the treatment of asthma – a disease of inflammation, not just bronchoconstriction
- In mild asthma PRN ICS-LABA is superior to PRN SABA with regards to both asthma control and reduction of risk of exacerbation.
- Single maintenance and reliever therapy- shown to decrease exacerbations- is endorsed by NIH/NAEPP guidelines for the first time, but is not a new approach

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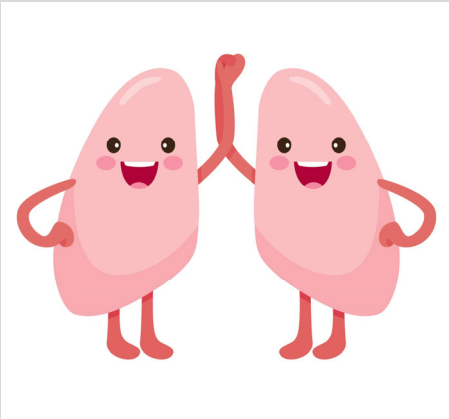

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Uncontrolled asthma

Includes difficult-to-treat and severe asthma

1. **Poor symptom control**
2. **Frequent severe exacerbations:**
   - ≥2 episodes of OCS/year
   - ≥1 hospitalization/ICU stay, or need for MV
3. **Post-BD airflow limitation**

Chung KF et al. ERJ 2014.

Difficult-to-treat vs. Severe asthma

Uncontrolled asthma or asthma requiring:
a) medium/high dose ICS + leukotriene modifier, or
b) OCS ≥50% of previous year

↓

Improvement after addressing **comorbidities and confounders**?

Yes → **Difficult-to-treat**

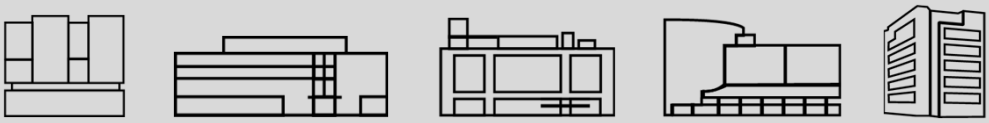
No → **Severe asthma**

Chung KF et al. ERJ 2014.
GINA 2020.

Difficult-to-treat asthma

Considerations in the challenging asthmatic

Medication compliance/adherence



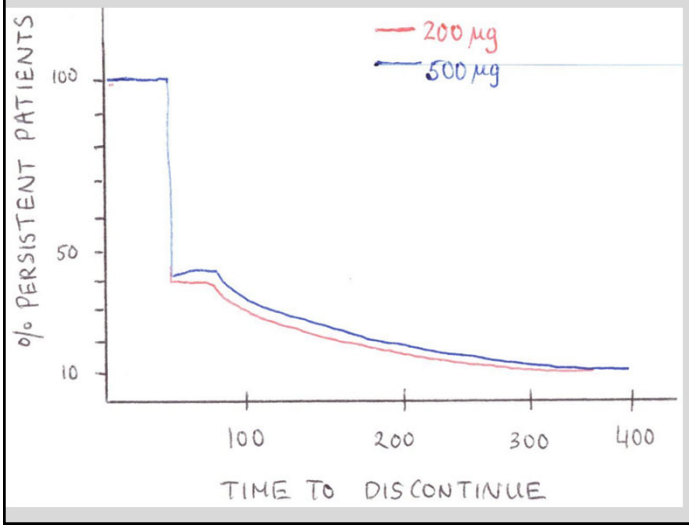
Fluticasone/salmeterol

Gamble J et al. Respir Med 2011.
Robinson DS et al. ERJ 2003.
Bender BG et al. JACI 2006.

Difficult-to-treat asthma

Considerations in the challenging asthmatic

Medication compliance/adherence



By year's end **only 8.8% of patients continued to refill inhaler script!**

Lower adherence factors:

♀

Age <35 yo

Copay >$10

Gamble J et al. Respir Med 2011.
Robinson DS et al. ERJ 2003.
Bender BG et al. JACI 2006.

Difficult-to-treat asthma

Considerations in the challenging asthmatic

Inhaler regimen complexity

Difficult-to-treat asthma

Considerations in the challenging asthmatic

Poor inhaler technique!

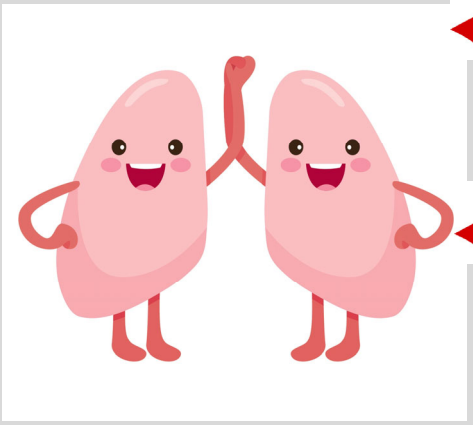
Difficult-to-treat asthma

TABLE 7 - Comorbidities and contributory factors
1) Rhinosinusitis/nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety
3) Vocal cord dysfunction
4) Obesity
5) **Smoking**/smoking related disease
6) **Obstructive sleep apnea**
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause
9) GERD
10) Drugs: aspirin, NSAIDs, b-adrenergic blockers, ACE-inhibitors

***Atopy/allergies:** Severe asthma potentially less associated with atopy/allergies vs. milder asthma.

Chung KF et al. ERJ 2014.
ENFUMOSA Study Group. ERJ 2003.

Objectives

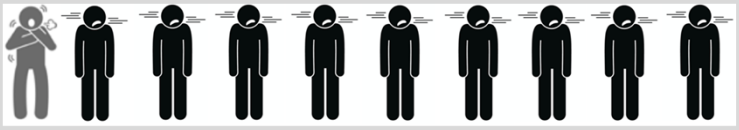


- ✓ Describe outcomes in asthma patients with COVID- 19
- ✓ Apply updated evidence and guideline recommendations in the management of mild asthma, with a focus on SMART therapy
- ✓ Identify and differentiate difficult-to-treat asthma from severe asthma
- Understand the significance of asthma phenotypes and the role of biologic therapies in the treatment of severe asthma

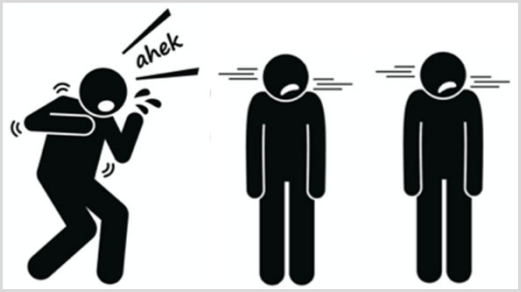
Severe asthma

A heterogenous disease, with variable clinical course and response to therapies

3-10% of asthmatics have severe asthma

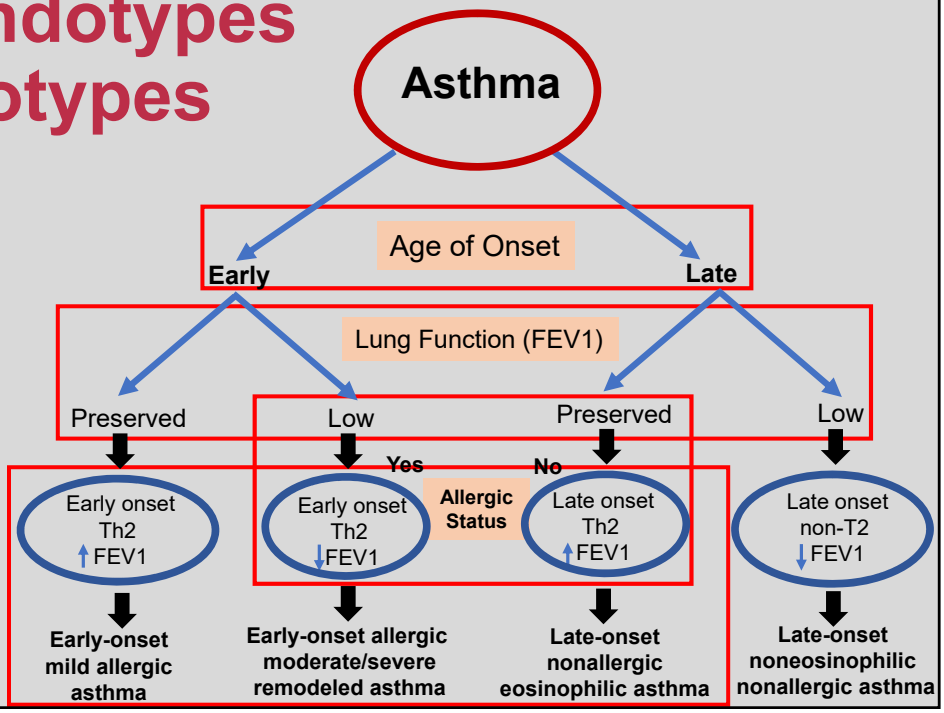


~30% of severe asthmatics require maintenance OCS



Chung KF et al. ERJ 2014.
Kaur and Chupp. JACI 2019.

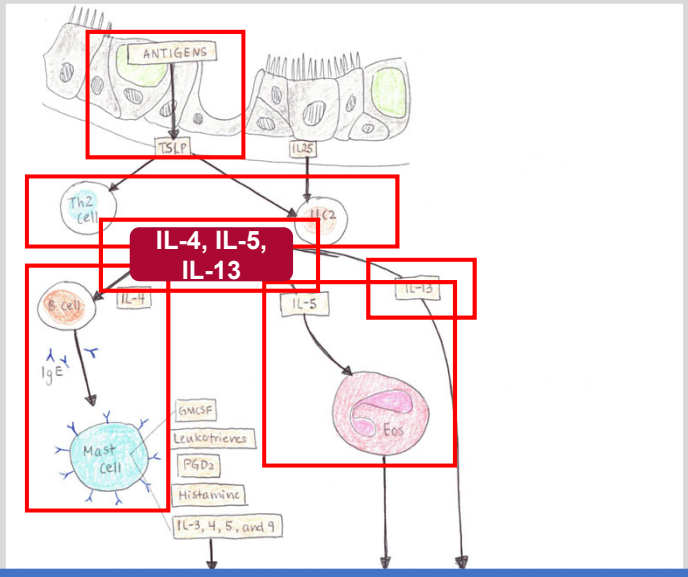
Asthma endotypes & phenotypes



Ravdeep Kaur, Geoffrey Chupp,
Phenotypes and endotypes of adult asthma:
Moving toward precision medicine,
Journal of Allergy and Clinical Immunology
https://doi.org/10.1016/j.jaci.2019.05.031.

Kaur and Chupp. JACI 2019.
Moore WC et al. AJRCCM 2010.
Haldar P et al. AJRCCM 2014.
Lefaudeux D et al. JACI 2017.

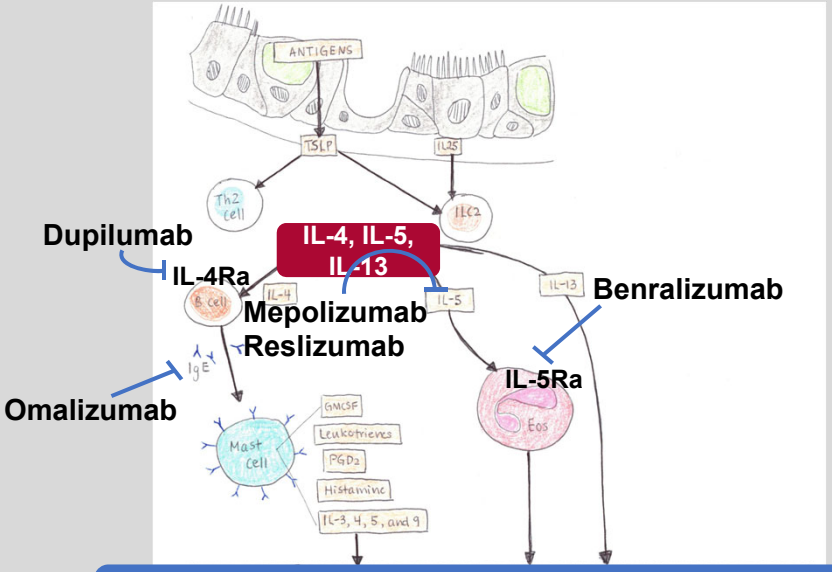
Severe asthma: T2-high



Hyperresponsiveness, remodeling, mucus production and smooth muscle constriction and hypertrophy

Israel E and Reddel HK. NEJM 2017.

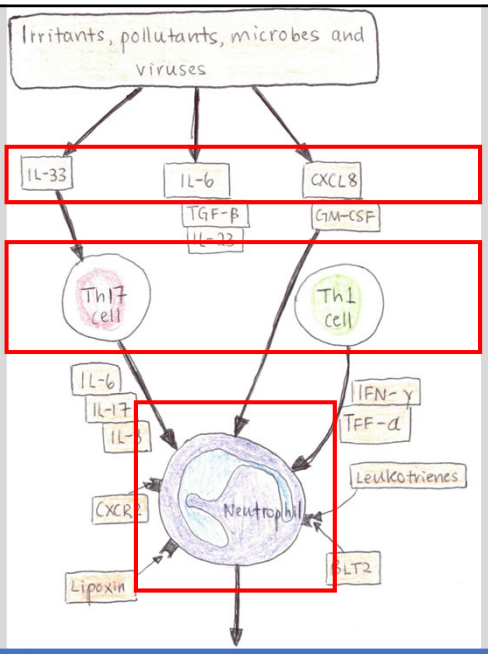
Severe asthma: T2-high targets



Hyperresponsiveness, remodeling, mucus production and smooth muscle constriction and hypertrophy

Israel E and Reddel HK. NEJM 2017.

Severe asthma: T2-low

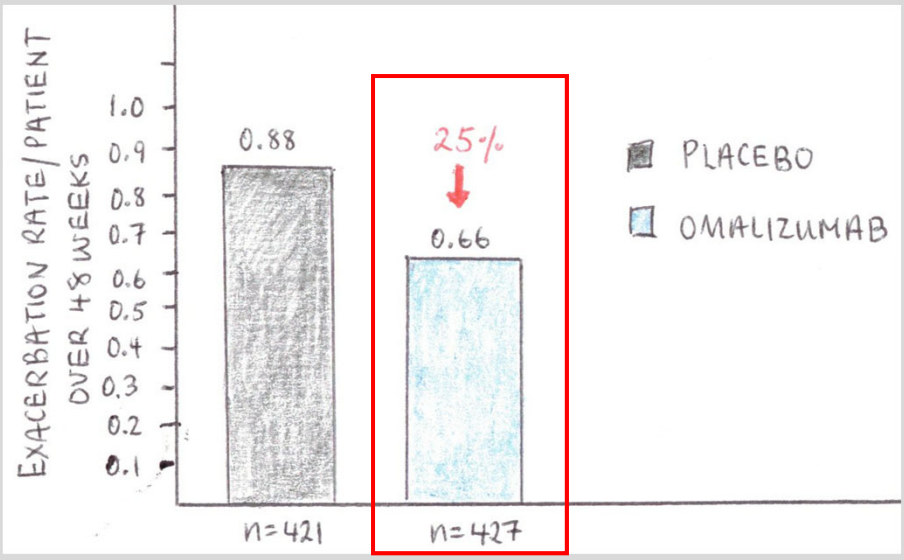


Israel E and Reddel HK. NEJM 2017.

Hyperresponsiveness, remodeling, mucus production and smooth muscle constriction and hypertrophy

Anti-IgE monoclonal antibody: Omalizumab

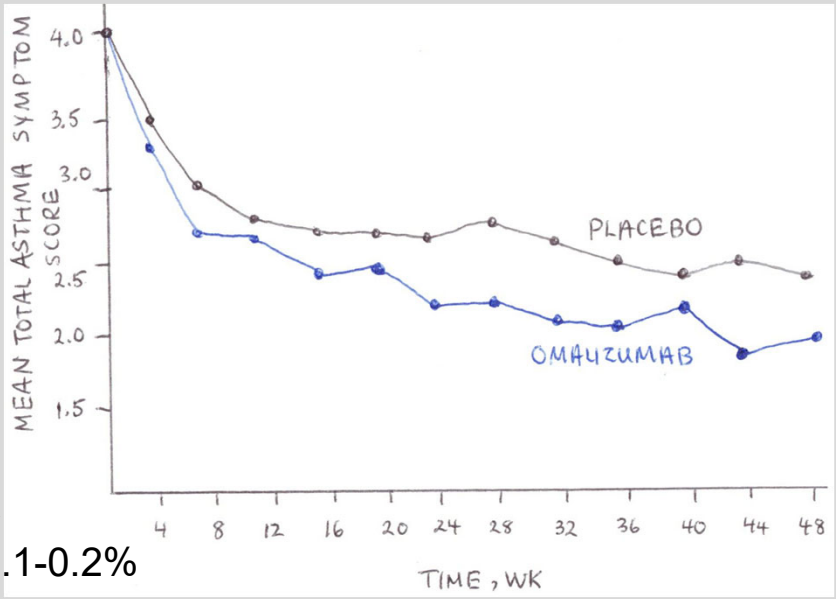
Asthma exacerbations over 48-week treatment period



Hanania NA et al. Ann Intern Med 2011.
Mcgregor MC et al. AJRCCM 2018.

Anti-IgE monoclonal antibody: Omalizumab

Significantly lower asthma symptom score with omalizumab



Indication: Allergic moderate/severe asthma

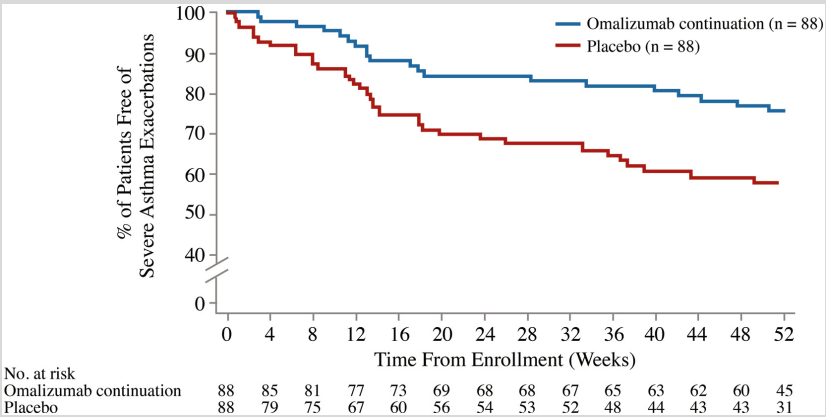
Major AE: Anaphylaxis 0.1-0.2%

Hanania NA et al. Ann Intern Med 2011.
Mcgregor MC et al. AJRCCM 2018.

Anti-IgE monoclonal antibody: Omalizumab

A randomized multicenter study evaluating Xolair persistence of response after long-term therapy

Dennis Ledford, MD,[a] William Busse, MD,[b] Benjamin Trzaskoma, MS,[c] Theodore A. Omachi, MD, MBA,[c] Karin Rosén, MD,[c] Bradley E. Chipps, MD,[d] Allan T. Luskin, MD,[e] and Paul G. Solari, MD[c] *Tampa, Fla, M*



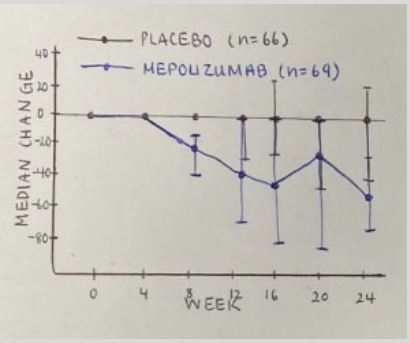
Significantly fewer severe asthma exacerbations when omalizumab continued

Ledford D et al. JACI 2017. Journal of Allergy and Clinical Immunology, ISSN: 0091-6749, Vol: 140, Issue: 1, Page: 162-169.e2

Anti-IL-5/anti-IL-5R: Mepolizumab, Reslizumab, Benralizumab

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma (SIRIUS)

Elisabeth H. Bel et al, NEJM 2014



Mepo group had 50% reduction in OCS dose

Bel EH. NEJM 2014.
McGregor et al. AJRCCM 2018.

Anti-IL-5/anti-IL-5R: Mepolizumab, Reslizumab, Benralizumab

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma (SIRIUS)

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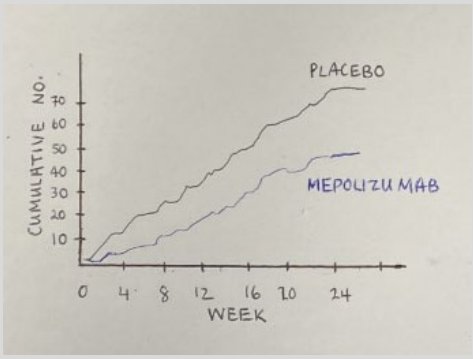


Bel EH. NEJM 2014.
McGregor et al. AJRCCM 2018.

Relative reduction 32% in asthma exacerbations with mepolizumab

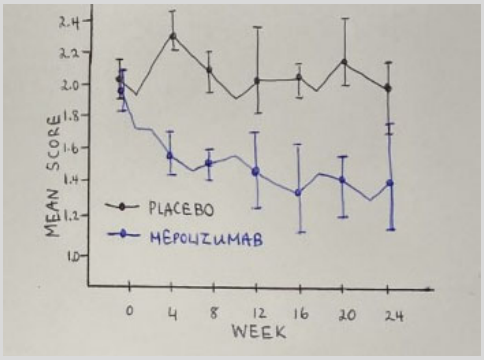
Anti-IL-5/anti-IL-5R: Mepolizumab, Reslizumab, Benralizumab

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma (SIRIUS)

Elisabeth H. Bel et al, NEJM 2014

Indication: Severe eosinophilic asthma

Major AEs:
Rare hypersensitivity reactions
Reactivation of zoster



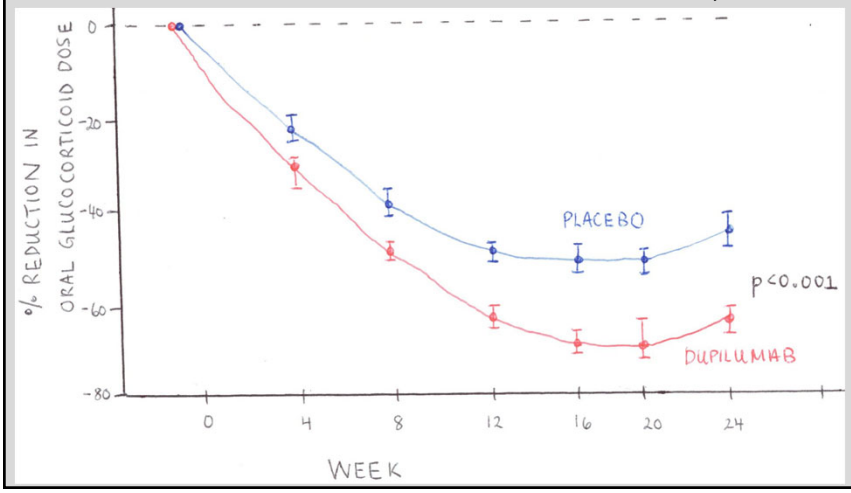
Significantly improved asthma-QOL with mepolizumab

Bel EH. NEJM 2014.
McGregor et al. AJRCCM 2018.

Anti-IL-4/IL-13: Dupilumab

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F Rabe et al, NEJM 2018



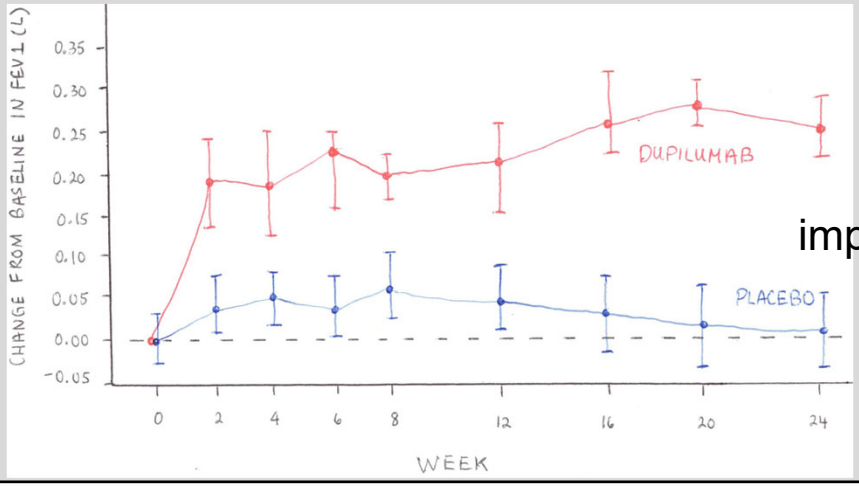
~70% reduction in OCS (dupilumab) vs. 42% with placebo

Rabe KF et al. NEJM 2018.
McGregor et al. AJRCCM 2018.

Anti-IL-4/IL-13: Dupilumab

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

Klaus F Rabe et al, NEJM 2018



220 mL improvement in FEV1

Rabe KF et al. NEJM 2018.
McGregor et al. AJRCCM 2018.

Anti-IL-4/IL-13: Dupilumab

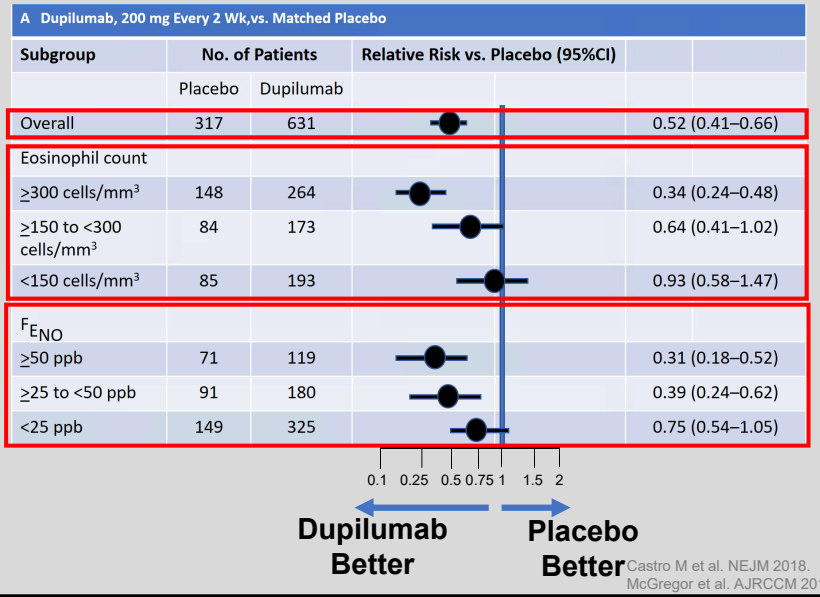
Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

Mario Castro et al, NEJM 2018

46% lower rate of severe asthma exac with dupilumab vs. placebo

Indications:
Severe eosinophilic or OCS-dependent asthma

Major AEs:
Rare hypersensitivity reactions
Hypereosinophilia

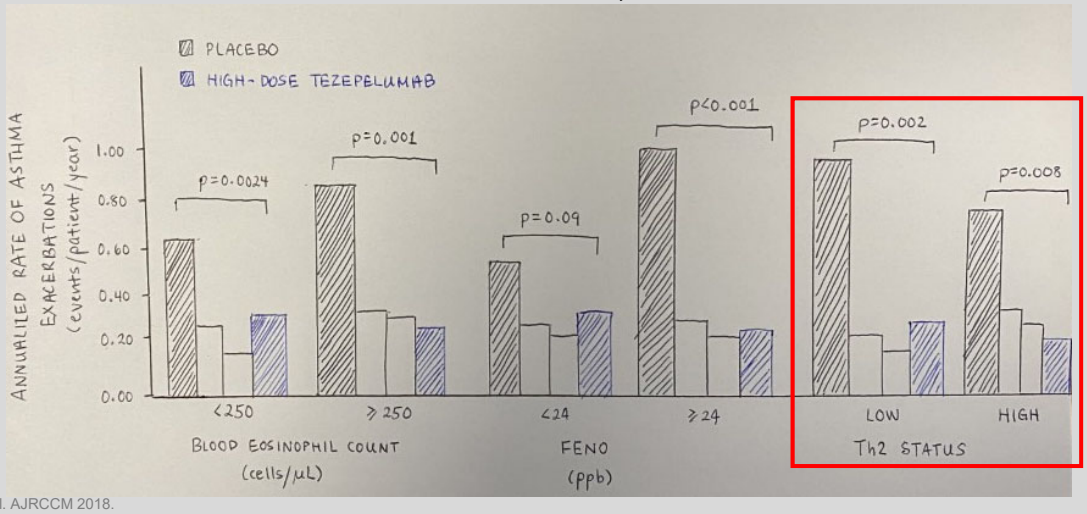


Castro M et al. NEJM 2018.
McGregor et al. AJRCCM 2018.

Severe asthma: What's next?

Tezepelumab in Adults with Uncontrolled Asthma

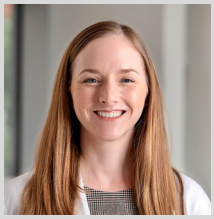
Jonathan Corren et al, NEJM 2017.



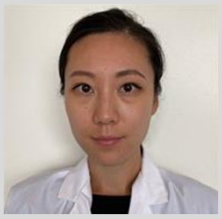
McGregor et al. AJRCCM 2018.
Corren J et al. NEJM 2017.

Summary
Take home messages

- **Exposure to ICS is key** in treatment of asthma – a disease of inflammation, not just bronchoconstriction.
- **ICS/Formoterol used PRN in mild asthma reduces risk for exacerbations**, without forsaking control.
- Single maintenance + reliever therapy newly endorsed by NIH/NAEPP guidelines, but not a new approach.
- Important to differentiate **difficult-to-treat** from **severe asthma**.
- For severe asthma, **biologic therapy may significantly reduce asthma exacerbations, reduce OCS need**, and improve symptoms/lung function.



Megan Conroy, MD
@DrMeganConroy



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Director
Jon Parsons, MD

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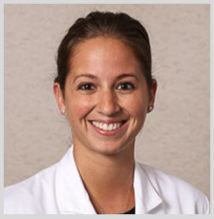

Jennifer McCallister,

Avi Cooper, MD

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