Stanford MEDICINE | Division of Primary Care and Population Health
Department of Medicine

Updates in Asthma Treatment

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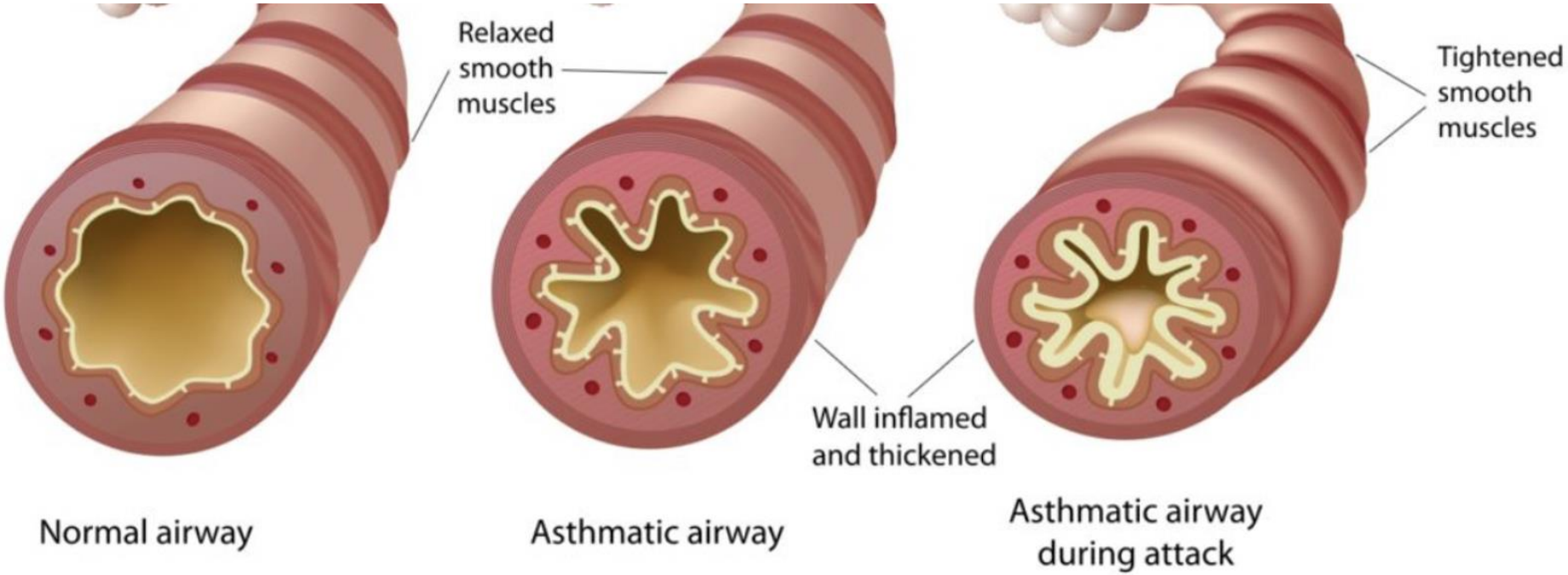
No financial disclosures

Serious Consequences

- 9.8 million office visits
- 1.8 million ER visits
- 3,564 deaths

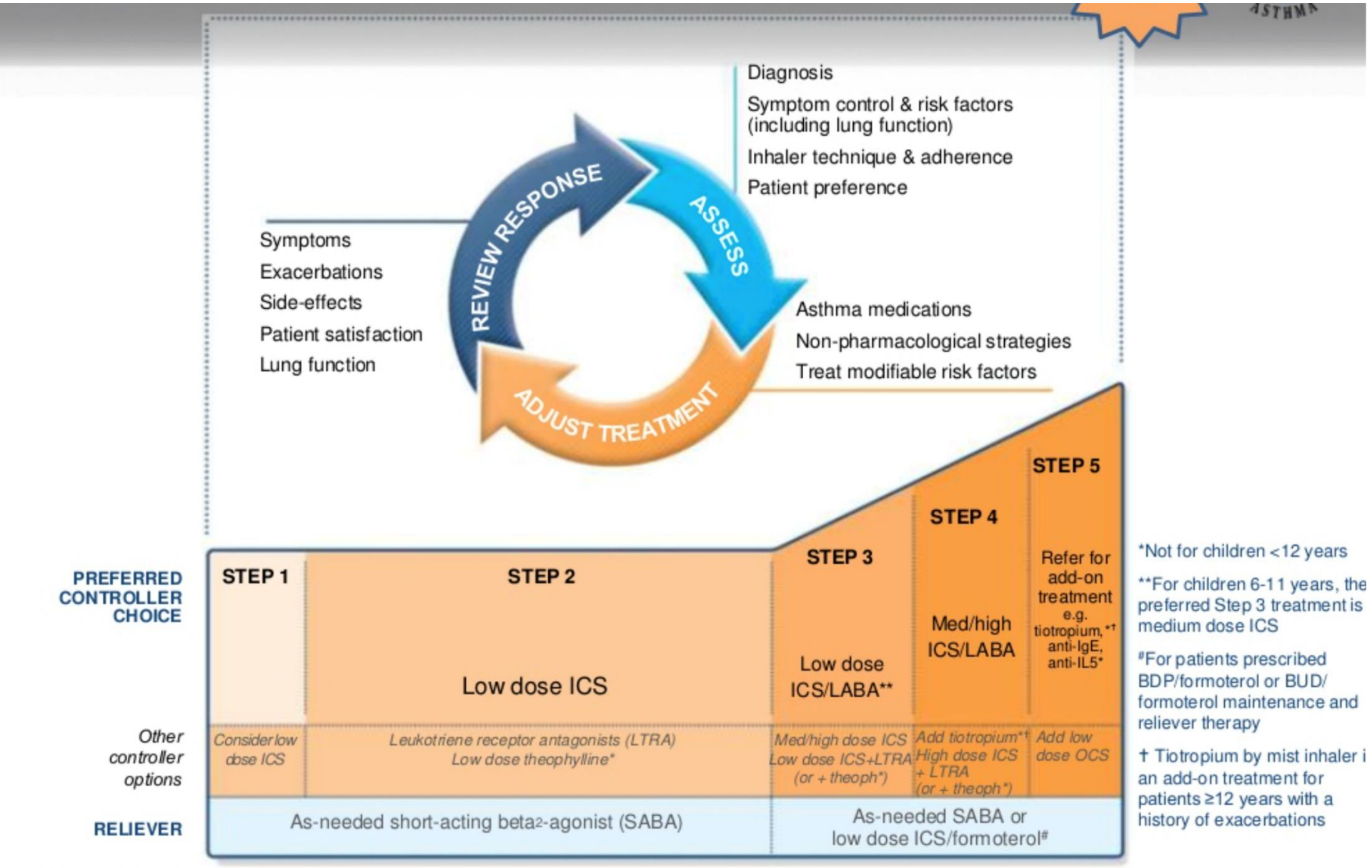
- African-Americans 3X more likely to die

Bronchospasm + Inflammation



SABA	Short acting beta agonist albuterol, terbutaline
LABA	Long acting beta agonist formoterol, salmetorol
ICS	Inhaled corticosteroid budesonide, fluticasone, beclomethasone, mometasone

Asthma: Pre-2017



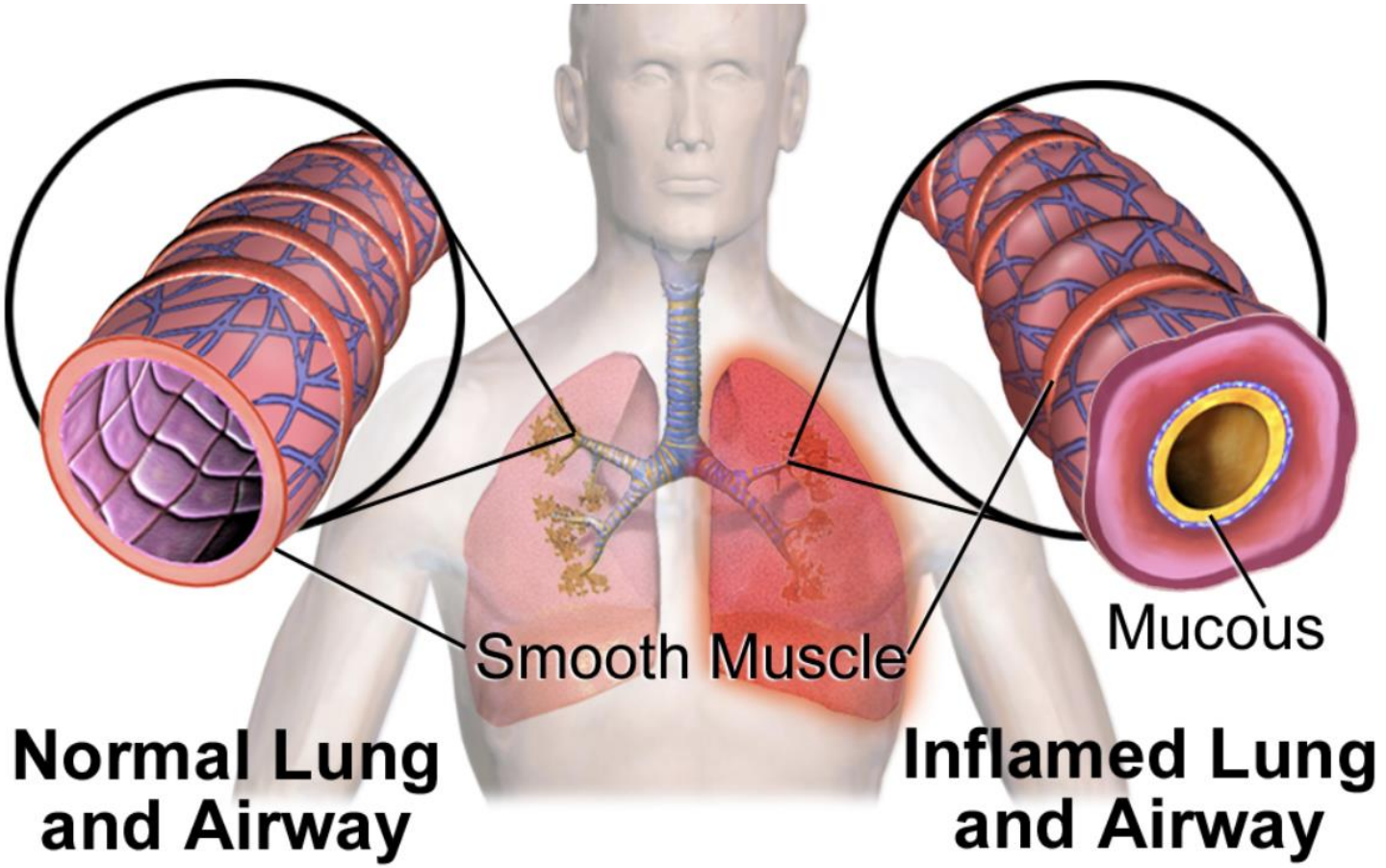
Revolution in Asthma: 2019

GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Why?

- Patient like the immediate effects SABA
- Providers use them for acute treatment
- **More than bronchoconstriction**



The Risks of "Mild" Asthma

Acute asthma exacerbations	30-37% “mild”
Dying of asthma	15-20% “mild”

Symptoms < weekly in previous 3 months

Dusser, Allergy 2007

More SABA use…

More adverse outcomes

- ≥3 canisters per year (average 1.7 puffs/day) is associated with higher risk of ED visits[1]
- ≥12 canisters per year is associated with higher risk of death[2]

[1]Stanford, AAAI 2012

[2]Suissa, AJRCCM 1994

Risks with SABA-only Treatment

Regular or frequent use of SABA is associated with adverse effects

- **B-receptor down regulation**
- **Decreased bronchodilator response[1]**

[1]Hancox, Respir Med 2000

Risks with SABA-only Treatment

Regular or frequent use of SABA is associated with adverse effects

- B-receptor down regulation
- Decreased bronchodilator response[1]

- **Rebound hyper responsiveness**
- **Increased allergic response and increased eosinophilic airway inflammation[2]**

[1]Hancox, Respir Med 2000

[2]Aldridge, AJRCCM 2000

Symbicort Given as Needed in Mild Asthma SYGMA 1 Trial

3,849 patients

Double blind RCT

Placebo controlled

52 weeks

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

ABSTRACT

BACKGROUND

In patients with mild asthma, as-needed use of an inhaled glucocorticoid plus a fast-acting β_2-agonist may be an alternative to conventional treatment strategies.

METHODS

We conducted a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma. Patients were randomly assigned to one of three regimens: twice-daily placebo plus terbutaline (0.5 mg) used as needed (terbutaline group), twice-daily placebo plus budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed (budesonide–formoterol group), or twice-daily budesonide (200 μg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide–formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.

RESULTS

A total of 3849 patients underwent randomization, and 3836 (1277 in the terbutaline group, 1277 in the budesonide–formoterol group, and 1282 in the budesonide maintenance group) were included in the full analysis and safety data sets. With respect to the mean percentage of weeks with well-controlled asthma per patient, budesonide–formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046) but inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; odds ratio, 0.64; 95% CI, 0.57 to 0.73). The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide–formoterol, and 0.09 with budesonide maintenance therapy; the rate ratio was 0.36 (95% CI, 0.27 to 0.49) for budesonide–formoterol versus terbutaline and 0.83 (95% CI, 0.59 to 1.16) for budesonide–formoterol versus budesonide maintenance therapy. The rate of adherence in the budesonide maintenance group was 78.9%. The median metered daily dose of inhaled glucocorticoid in the budesonide–formoterol group (57 μg) was 17% of the dose in the budesonide maintenance group (340 μg).

CONCLUSIONS

In patients with mild asthma, as-needed budesonide–formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed according to electronically recorded weeks with well-controlled asthma, but was inferior to budesonide maintenance therapy. Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide–formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy. (Funded by AstraZeneca; SYGMA 1 ClinicalTrials.gov number, NCT02149199.)

From the Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON (P.M.O.), and the Institute for Heart and Lung Health, University of British Columbia, Vancouver (J.M.F.) — both in Canada; the Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa (E.D.B.); Airway Disease Section, National Heart and Lung Institute, Imperial College, London (P.J.B.); State Key Laboratory of Respiratory Diseases, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China (N.Z.); AstraZeneca Research and Development, Gothenburg, Sweden (C.K., C.J., S.I.); AstraZeneca Research and Development, Barcelona (R.L.); and Woolcock Institute of Medical Research, University of Sydney, Sydney (H.K.R.). Address reprint requests to Dr. O'Byrne at the Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, McMaster University, Rm. 2E1, 1280 Main St. West, Hamilton, ON L8S 4K1, Canada, or at obyrnep@mcmaster.ca.

N Engl J Med 2018;378:1865-76.
DOI: 10.1056/NEJMoa1715274

Symbicort Given as Needed in Mild Asthma (SYGMA) 1

Budesonide daily + Terbutaline PRN

Terbutaline PRN

Budesonide + Formoterol PRN

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SYGMA 1 Trial Findings

	Better asthma-symptom control weeks
Budesonide daily + Terbutaline PRN	44 %
Terbutaline PRN	31 %
Budesonide + Formoterol PRN	34 %

SYGMA 1 Trial Findings

	Better asthma-symptom control weeks	Annual rate of severe exacerbations
Budesonide daily + Terbutaline PRN	44 %	0.09
Terbutaline PRN	31 %	0.20
Budesonide + Formoterol PRN	34 %	0.07

Findings SYGMA 1

Budesonide-Formoterol PRN

vs

Terbutaline PRN

64% lower rate
of severe exacerbations

SYGMA 1 Trial Findings

	Better asthma-symptom control weeks	Annual rate of severe exacerbations	ICS
Budesonide daily + Terbutaline PRN	44 %	0.09	100
Terbutaline PRN	31 %	0.20	0
Budesonide + Formoterol PRN	34 %	0.07	17%

Findings SYGMA 1

Budesonide-Formoterol PRN

vs

Budesonide daily

PRN associated with 83% lower cumulative dose of ICS

SYGMA 2 Trial: Mild Asthma

4,215 patients

Double blind

52 weeks

- **Similar reduction in the risk of severe exacerbations for PRN ICS-formoterol vs daily budesonide**

- **75% less corticosteroid in PRN budesonide-formoterol vs daily budesonide**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D., Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

ABSTRACT

BACKGROUND

Patients with mild asthma often rely on inhaled short-acting β_2-agonists for symptom relief and have poor adherence to maintenance therapy. Another approach might be for patients to receive a fast-acting reliever plus an inhaled glucocorticoid component on an as-needed basis to address symptoms and exacerbation risk.

METHODS

We conducted a 52-week, double-blind, multicenter trial involving patients 12 years of age or older who had mild asthma and were eligible for treatment with regular inhaled glucocorticoids. Patients were randomly assigned to receive twice-daily placebo plus budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed or budesonide maintenance therapy with twice-daily budesonide (200 μg)

More Supporting Evidence

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

THE LANCET
Volume 394, Issue 10202, 14–20 September 2019, Pages 919-928

Articles

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Confirmed: Fewer Adverse Events

Landmark Changes in Asthma Treatment

Global Initiative for Asthma (GINA 2019)

For safety, do not use SABA-only treatment for Step 1

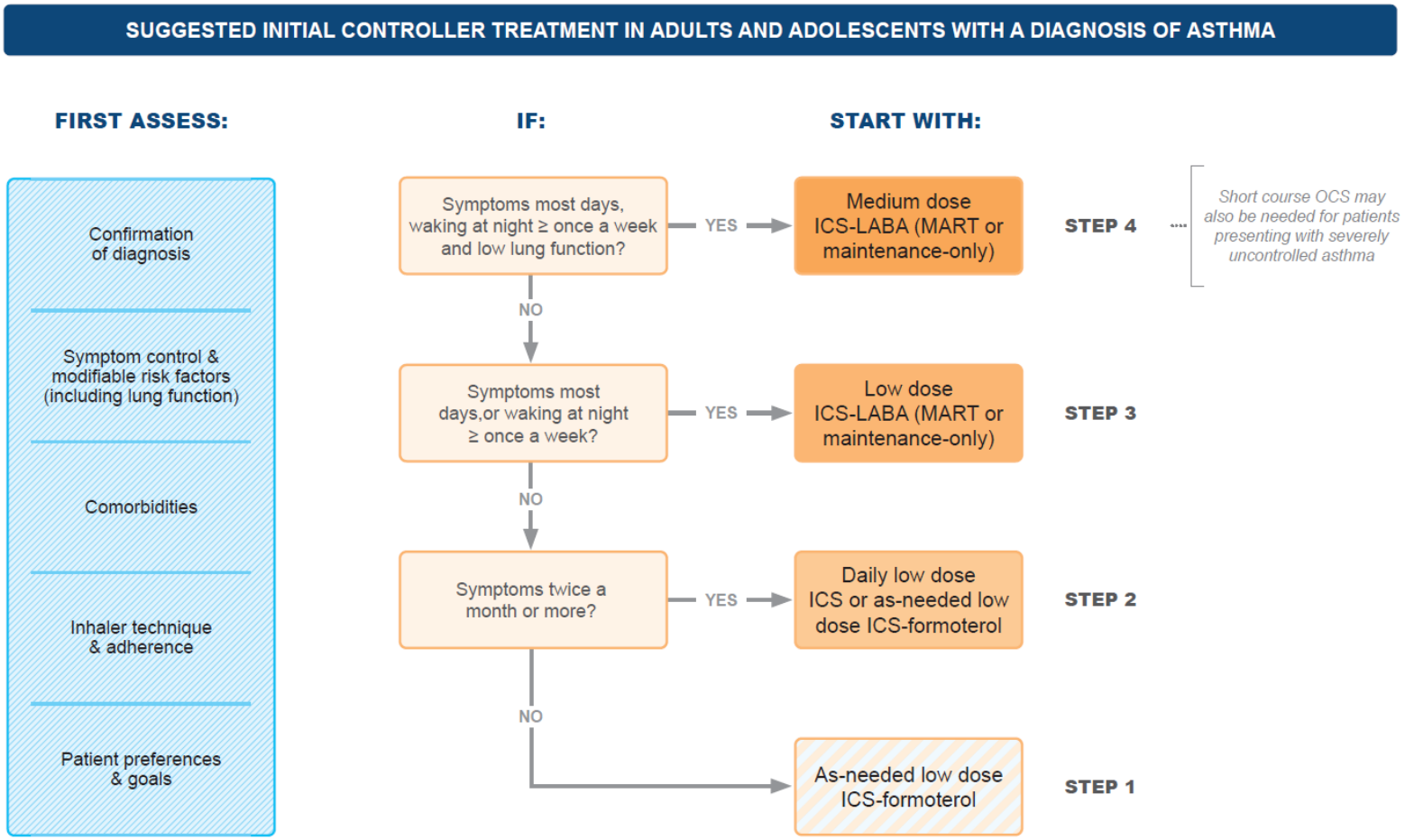
- SABA-only treatment increases the risk of severe exacerbations
- Adding any ICS significantly reduces risk

Instead, use ICS-containing controller treatment:

- ICS daily treatment or
- In mild asthma, PRN ICS-formoterol

Reduce Serious Exacerbations

Starting Treatment

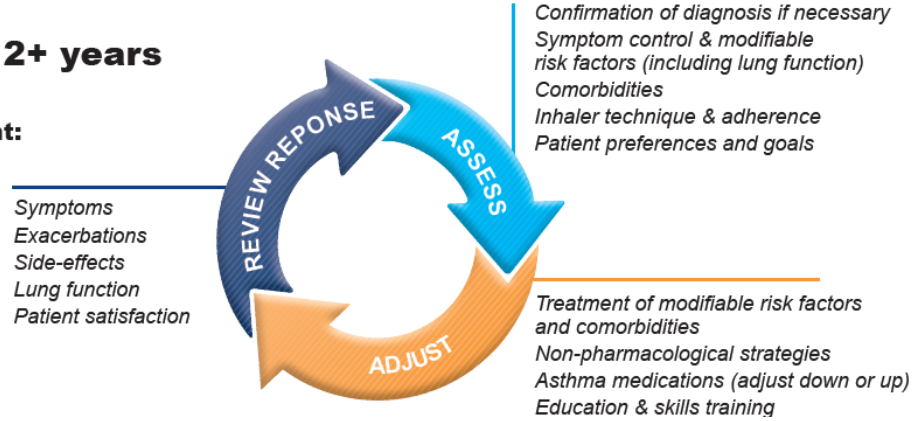


Adjusting Treatment

Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response



Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1		
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *		
Other controller options	*Low dose ICS taken whenever SABA is taken †*		
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy‡
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*		

* *Data only with budesonide-formoterol (bud-form)*
† *Separate or combination ICS and SABA inhalers*
‡ *Low-dose ICS-form is the reliever only for patients prescribed bud-form or BDP-form maintenance and reliever therapy*
\# *Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted*

Adjusting Treatment

Box 3-5A

Adults & adolescents 12+ years

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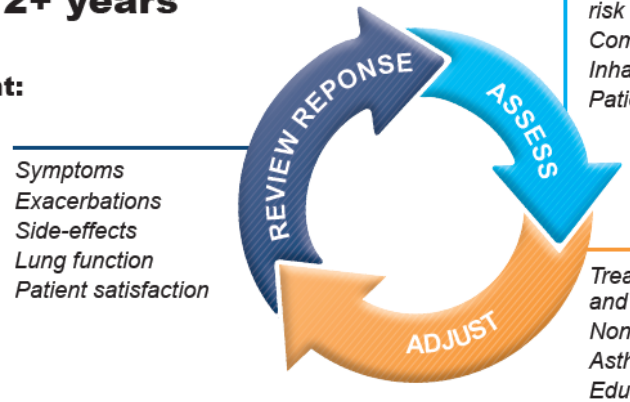
Assess, Adjust, Review response



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
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 or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual patient needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	As-needed low dose ICS-formoterol *	Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *	Low dose ICS-LABA	Medium dose ICS-LABA	High dose ICS-LABA Refer for phenotypic assessment ± add-on therapy, e.g.tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
Other controller options	*Low dose ICS taken whenever SABA is taken †*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †*	*Medium dose ICS, or low dose ICS+LTRA #*	*High dose ICS, add-on tiotropium, or add-on LTRA #*	*Add low dose OCS, but consider side-effects*
PREFERRED RELIEVER	As-needed low dose ICS-formoterol *		As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy‡		
Other reliever option	*As-needed short-acting β_2-agonist (SABA)*				

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\# *Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV1 >70% predicted*

ICS Dosing

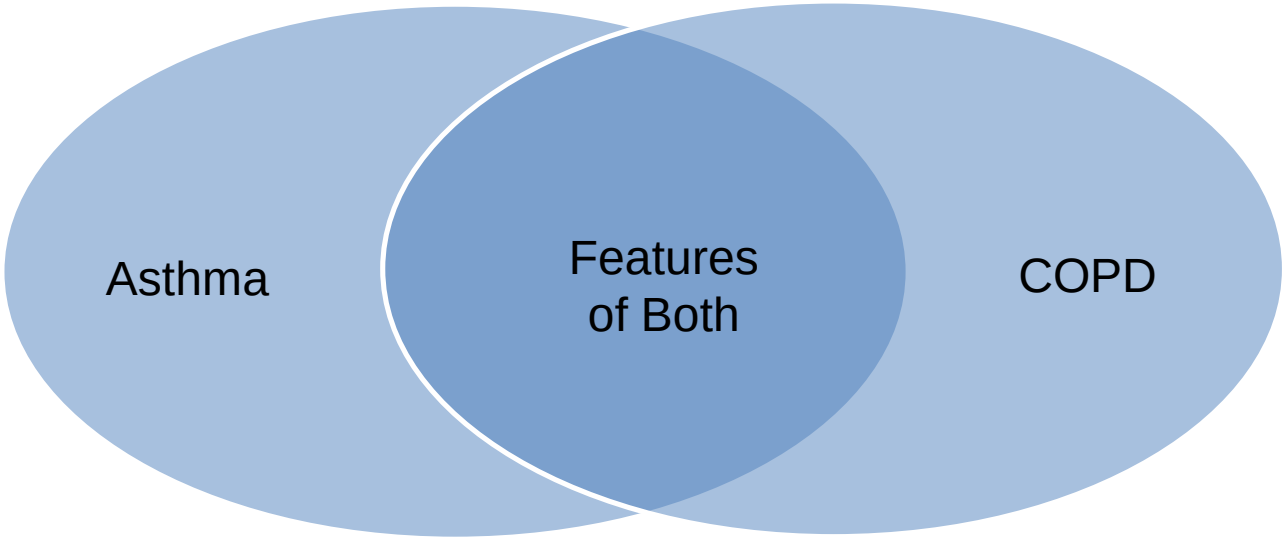
- **Low dose ICS provides most of the clinical benefit of ICS for <u>most patients</u> with asthma**

Decreasing Oral Corticosteroid Dependence

Biologics

Drug	Target	Criteria	Administration
Omalizumab (Xolair)	Anti-IgE	IgE 30-700 One perennial allergen, no exacerbation requirement	SQ q 2-4 weeks based on IgE level and weight
Mepolizumab (Nucala)	IL-5	>150 eosinophils >2 exacerbations past year	100mg SQ q 4 weeks
Reslizumab (Cinqair)	IL-5	>400 eosinophils, >1 exacerbation past year	3mg/kg IV q 4 weeks
Benralizumab (Fasenra)	IL-5R	>300 eosinophils, >2 exacerbation past year	30mg SQ q 4 weeks x 3 doses then q 8 weeks
Dupilumab (Dupixent)	IL4R	>150 eosinophils or >3% sputum eosinophils and >1 exacerbation in the past year, or chronic steroids	2 does of 200mg or 300mg SQ 1st week then 1 dose q 2 weeks (higher dose if steroid dependent asthma, severe atopic dermatitis)

Asthma-COPD Overlap



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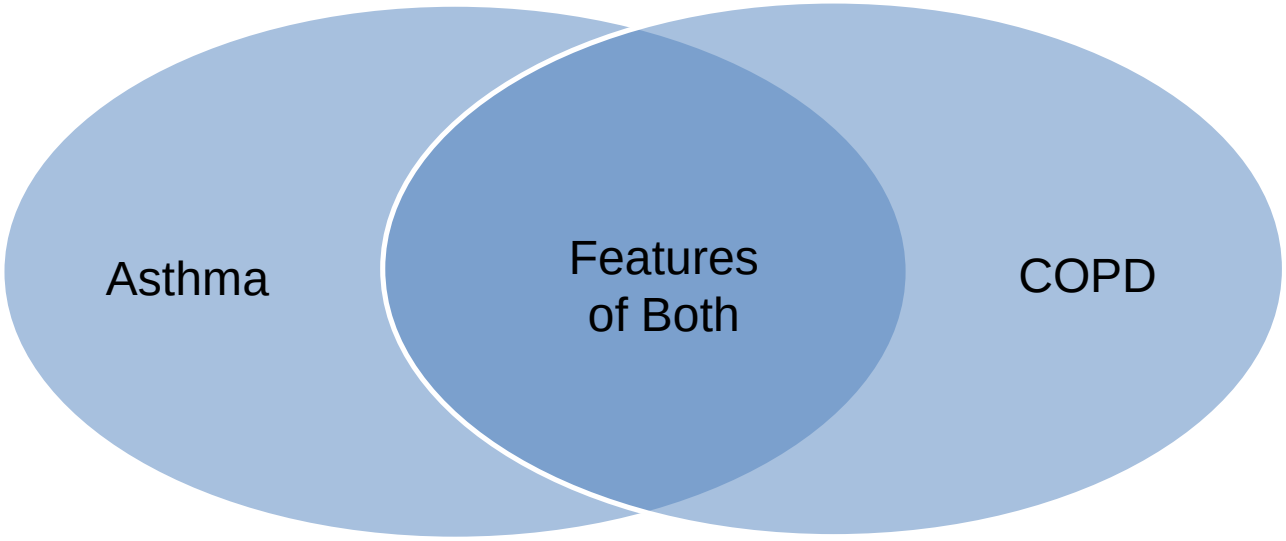


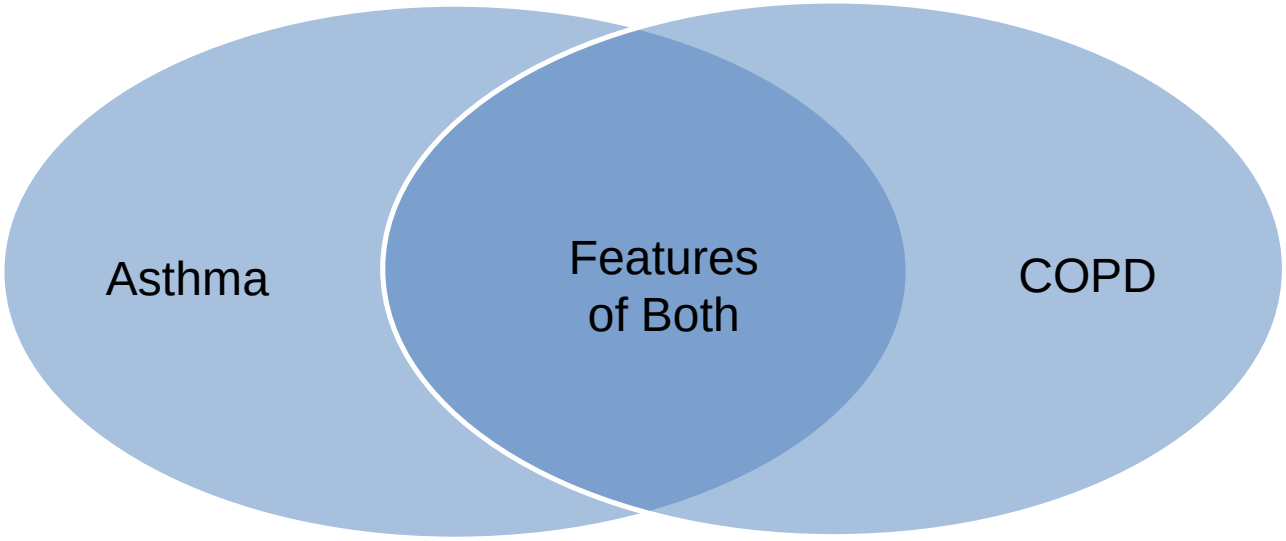
Variable symptoms
Triggers
Earlier age onset
Respond to BD in minutes
Respond to ICS days to weeks

Variable expiratory airflow limitation

Age onset after 40
Persistent Dyspnea
Activity limited
+/- BD response
Toxic exposure/hx smoking

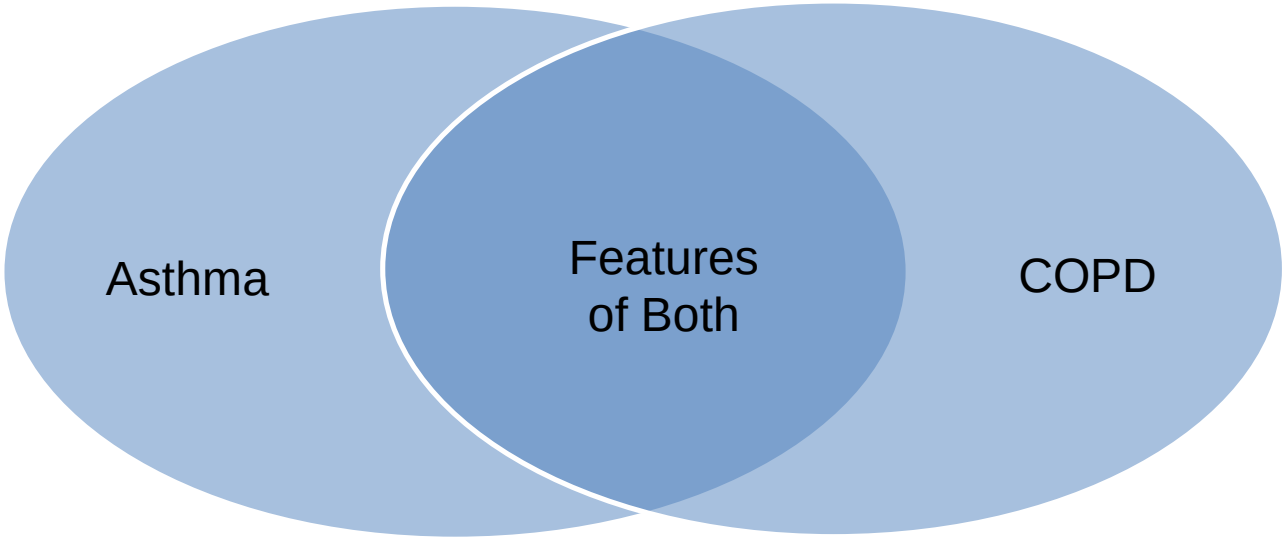
Persistent expiratory airflow limitation

Asthma-COPD Overlap



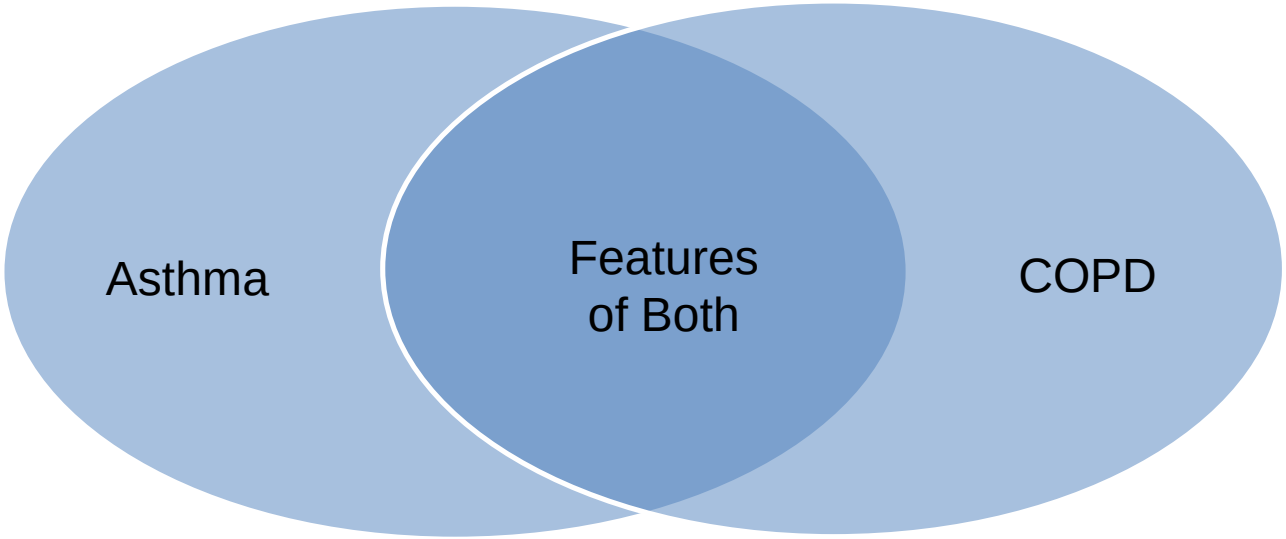
- GINA recommendations:
  - **Asthma: <u>never</u> treat with bronchodilators alone (risk of death, hospitalization, severe exacerbations)**

Asthma-COPD Overlap



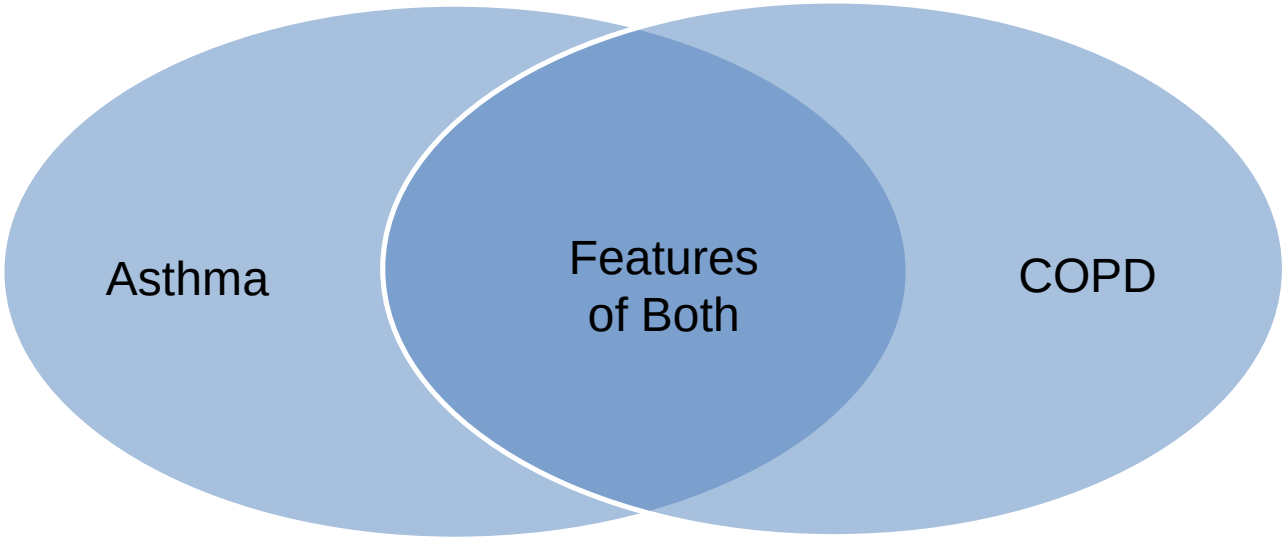
- GINA recommendations:
  - Asthma: <u>never</u> treat with bronchodilators alone (risk of death, hospitalization, severe exacerbations)
  - **COPD: <u>start</u> treatment with LABA and/or LAMA without ICS**

Asthma-COPD Overlap



- GINA recommendations:
  - Asthma: <u>never</u> treat with bronchodilators alone (risk of death, hospitalization, severe exacerbations)
  - COPD: <u>start</u> treatment with LABA and/or LAMA without ICS
  - **Patients with both asthma and COPD are more likely to die or be hospitalized if treated with LABA vs ICS-LABA** ***(Gershon et al, JAMA 2014; Kendzerska et al, Annals ATS 2019)***

Asthma-COPD Overlap



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  - COPD: <u>start</u> treatment with LABA and/or LAMA without ICS
  - Patients with both asthma and COPD are more likely to die or be hospitalized if treated with LABA vs ICS-LABA *(Gershon et al, JAMA 2014; Kendzerska et al, Annals ATS 2019)*
  - **High dose ICS may be needed for severe asthma, but should not be used in COPD (risk of pneumonia)**

Real Practice: COST and COVERAGE

- **ICS-LABA: More expensive, often not fully covered by insurance or with higher co-pays**

Real Practice: COST and COVERAGE

- ICS-LABA: More expensive, often not fully covered by insurance or with higher co-pays
- **Budesonide-formoterol covered by 9/10 insurance types -- co-pays can be high**

Real Practice: COST and COVERAGE

- ICS-LABA: More expensive, at times not fully covered by insurance or with higher co-pays
- Budesonide-formoterol advertises covered by 9/10 insurance types -- co-pays can be high
- **Option to use SABA and take ICS-low dose any time SABA used**

Black Box Warning with Montelukast

- **March 2020 FDA boxed warning about risk of serious neuropsychiatric events, including suicidality, depression and agitation**

FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis

Risks may include suicidal thoughts or actions

Black Box Warning with Montelukast

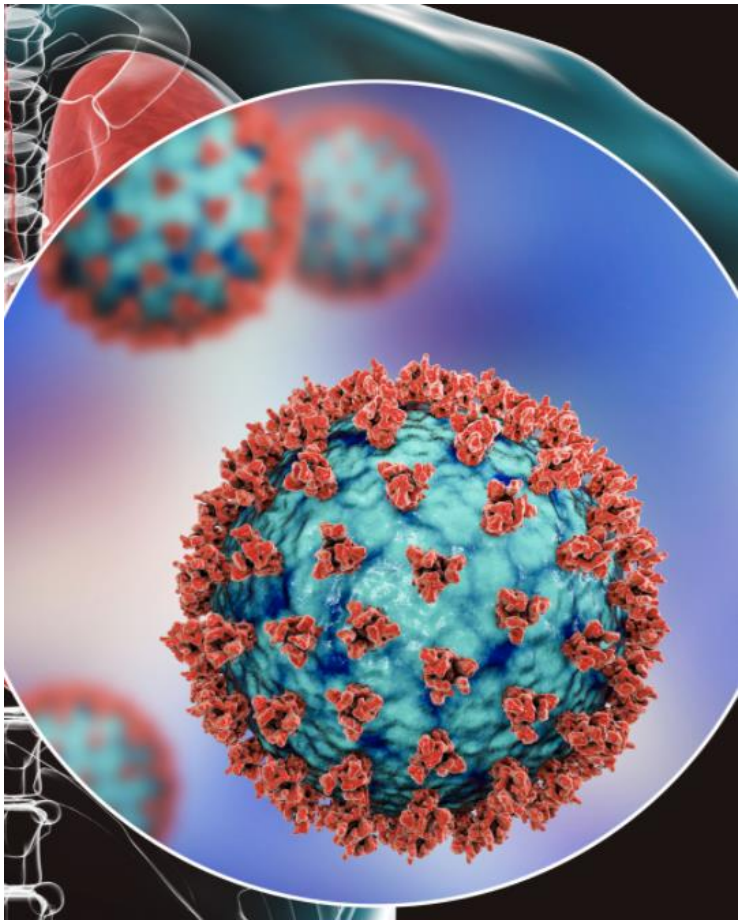
- March 2020 FDA boxed warning about risk of serious neuropsychiatric events, including suicidality, depression and agitation
- **Before prescribing Montelukast, consider its benefits and risks and other alternatives and counsel patients about the risk of neuropsychiatric events**

FDA requires Boxed Warning about serious mental health side effects for asthma and allergy drug montelukast (Singulair); advises restricting use for allergic rhinitis

Risks may include suicidal thoughts or actions

COVID-19 and Asthma

- Continue ICS, OCS, biologics
- Avoid nebulizers where possible
- Use MDI with spacer for severe exacerbations.
- **Avoid spirometry and peak flow in PUI or COVID**



Clinical pearls

- **SABAs do not treat the airway inflammation underlying asthma and are useful in the treatment of symptoms only**

Key Points

- SABAs do not treat the airway inflammation underlying asthma and are useful in the treatment of symptoms only
- **Avoid using short acting beta agonists alone in patients with mild asthma**

Key Points

- SABAs do not treat the airway inflammation underlying asthma and are useful in the treatment of symptoms only
- Avoid using short acting beta agonists alone in patients with mild asthma
- **Use ICS-containing inhaler to control mild asthma**


Thank you!