Updates in Asthma Treatment

Laura Vaughan, MD
Clinical Assistant Professor of Medicine
Stanford University

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Serious Consequences

- 9.8 million office visits
- 1.8 million ER visits
- 3,564 deaths
- African-Americans 3X more likely to die
Bronchospasm + Inflammation

Normal airway

Asthmatic airway

Asthmatic airway during attack
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA</td>
<td>Short acting beta agonist</td>
<td>albuterol, terbutaline</td>
</tr>
<tr>
<td>LABA</td>
<td>Long acting beta agonist</td>
<td>formoterol, salmeterol</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroid</td>
<td>budesonide, fluticasone, beclomethasone, mometasone</td>
</tr>
</tbody>
</table>
Asthma: Pre-2017

Pre-2017 management of asthma focused on a stepwise approach, which included:

1. **Preferred Controller Choice**
   - **Low dose ICS**
   - Consider low dose ICS
   - Leukotriene receptor antagonists (LTRA)
   - Low dose theophylline

2. **Other controller options**
   - As-needed short-acting beta2-agonist (SABA)

3. **Step 2**
   - **Low dose ICS/LABA**
   - Leukotriene receptor antagonists (LTRA)
   - Low dose theophylline

4. **Step 3**
   - **Med/high ICS/LABA**
   - Med/high dose ICS
   - Low dose ICS + LTRA (or + theoph)
   - Add tiotropium
   - High dose ICS + LTRA (or + theoph)

5. **Step 4**
   - Refer for add-on treatment e.g. anti-IgE, anti-IL5
   - Tiotropium by mist inhaler

6. **Step 5**
   - As-needed SABA or low dose ICS/formoterol

**Notes:**
- Not for children <12 years
- For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
- For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
- Tiotropium by mist inhaler an add-on treatment for patients ≥12 years with a history of exacerbations
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

- **SABA ALONE**
- **ICS-formoterol PRN**
- **ICS Containing Inhaler daily**
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
Regular or frequent use of SABA is associated with adverse effects

- $\beta$-receptor down regulation
- Decreased bronchodilator response$^1$

$^1$Hancox, Respir Med 2000
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
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 Keens, M.D., Carin Jonup, M.D., Rosa Lar marca, 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 β₂-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 0.81 (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)
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

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Budesonide-Formoterol PRN
vs
Terbutaline PRN

64% lower rate of severe exacerbations
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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
More Supporting Evidence

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.,
and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

Confirmed: Fewer Adverse Events

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
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

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA

FIRST ASSESS:
- Confirmation of diagnosis
- Symptom control & modifiable risk factors (including lung function)
- Comorbidities
- Inhaler technique & adherence
- Patient preferences & goals

IF:
- Symptoms most days, waking at night ≥ once a week and low lung function? YES → Medium dose ICS-LABA (MART or maintenance-only)
  NO →
- Symptoms most days, or waking at night ≥ once a week? YES → Low dose ICS-LABA (MART or maintenance-only)
  NO →
- Symptoms twice a month or more? YES → Daily low dose ICS or as-needed low dose ICS-formoterol
  NO →

START WITH:
- As-needed low dose ICS-formoterol

STEP 1

STEP 2

STEP 3

STEP 4

[Note: Short course OCS may also be needed for patients presenting with severely uncontrolled asthma]
Adjusting Treatment

Box 3-5A
Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

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 or up)
Education & skills training

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

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER
Other reliever option

STEP 1
As-needed low dose ICS-formoterol *
Low dose ICS taken whenever SABA is taken †

As-needed low dose ICS-formoterol *
As-needed low dose ICS-formoterol for patients prescribed maintenance and reliever therapy ‡

As-needed short-acting β₂-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

Personalized asthma management:
Assess, Adjust, Review response

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

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to prevent exacerbations and control symptoms

Other controller options

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Other reliever option

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<th>STEP 2</th>
<th>STEP 3</th>
<th>STEP 4</th>
<th>STEP 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-needed low dose ICS-formoterol *</td>
<td>Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *</td>
<td>Low dose ICS-LABA</td>
<td>Medium dose ICS-LABA</td>
<td>High dose ICS-LABA</td>
</tr>
<tr>
<td>Low dose ICS taken whenever SABA is taken †</td>
<td>Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †</td>
<td>Medium dose ICS, or low dose ICS+LTRA #</td>
<td>High dose ICS, add-on tiotropium, or add-on LTRA #</td>
<td>Add low dose OCS, but consider side-effects</td>
</tr>
</tbody>
</table>

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Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

---

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

---

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* 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
ICS Dosing

- Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma
## Decreasing Oral Corticosteroid Dependence

### Biologics

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

Asthma

Features of Both

COPD
Asthma-COPD Overlap

Asthma

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

COPD

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

Features of Both

- Variable expiratory airflow limitation
- Persistent expiratory airflow limitation
GINA recommendations:

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

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

- Asthma: *never* treat with bronchodilators alone (risk of death, hospitalization, severe exacerbations)
- COPD: *start* 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*)
GINA recommendations:

- Asthma: never treat with bronchodilators alone (risk of death, hospitalization, severe exacerbations)

- COPD: start 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 \( \text{(Gershon et al, JAMA 2014; Kendzerska et al, Annals ATS 2019)} \)

- 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
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!