Two new asthma guidelines:

What is still true and how to make sense of the discordance

DATE: July, 2021   PRESENTED BY: Williams, Craig; Clinical Professor, williacr@ohsu.edu
Conflicts of Interest: None

Key Objectives:
- Revisit a couple aspects of asthma that continue to be true
- Consider the discordance of recent guideline updates which no longer completely agree

First, a little context....

NIH Report:
Guidelines for the Diagnosis and Management of Asthma
Summary report available online: http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.htm

COPD: Global Initiative for Chronic Obstructive Lung Disease (GOLD)
www.goldcopd.com
GINA 2019: Global INitiative for Asthma; concept behind GINA was to be a bit more nimble like the GOLD guidelines

Notable update in “What’s New”:

‘SABA only’ for prn intermittent no longer recommended
Key Objectives:

- Revisit a couple aspects of asthma that have always been true
  - Or at least true for a lot longer than the 2019-2020 guideline updates
Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma

APPENDIX

The members of the research group for the trial were as follows: Baylor College of Medicine, Houston — N.A. Hanania (principal investigator), M. Sockrider (coprincipal investigator), L. Giraldo (principal clinic coordinator), R. Valdez, E. Flores (coordinators); Columbia University—New York University Consortium, New York — J. Reibman (principal investigator), E. DiMango, L. Rogers (coprincipal investigators), C. Cammarata, K. Carapetyan (clinical coordinators at New York University), J. Sornilllon, E. Simpson (clinical coordinators at Columbia University); Duke University Medical Center, Durham, NC — L. Williams (principal investigator), J. Sundy (coprincipal investigator), G. Dudek (principal clinic coordinator), R. Newton, A. Dugdale (coordinators); Emory University School of Medicine, Atlanta — W.G. Teague (principal investigator), A. Fitzpatrick, S. Khatri (coprincipal investigators), R. Patel (principal clinic coordinator), J. Peabody, E. Hunter, D. Whitlock (coordinators); Illinois Consortium, Chicago — L. Smith (principal investigator), J. Moy, E. Nau, Olof Olofsson (coprincipal investigators), J. Hixon (principal clinic coordinator), A. Brees, G. Rivera, S. Sievers, V. Zagaja (coordinators); Indiana University, Asthma Clinical Research Center, Indianapolis — M. Busk (principal investigator), C. Williams (coprincipal investigator), P. Puntenney (principal clinic coordinator), N. Busk (coordinator); University of Pennsylvania, Philadelphia — F. Leone (principal investigator), M. Hayes-Hampton (principal clinic coordinator); Louisiana State University Health Sciences Center, New Orleans — S. Erwin (principal investigator), C. Kelleher (principal clinic coordinator), S. McMurphy, A. Warriner (coordinators); University of Miami—University of South Florida, Tampa — A. Wanner (principal investigator, Miami), R. Lockey (principal investigator, Tampa), E. Mendes (principal clinic coordinator for University of Miami), S. McPherson (principal clinic coordinator for University of South Florida), B. Fimbel, M. Grandstaff (coordinators); University of Minnesota, Minneapolis — M.N. Blumenfeld (principal investigator), G. Brozman, J. Hagen (coprincipal investigators), A. Decker, D. Lascowski, S. Kelleher (principal clinic coordinators), K. Bachman, C. Quintard, C. Sherry (coordinators); University of Missouri—Kansas City School of Medicine, Kansas City — G. Salzman (principal investigator), D.

CONCLUSIONS

Despite a high prevalence of asymptomatic gastroesophageal reflux among patients with poorly controlled asthma, treatment with proton-pump inhibitors does not improve asthma control. Asymptomatic gastroesophageal reflux is not a likely cause of poorly controlled asthma. (ClinicalTrials.gov number, NCT00069823.)
The 2007 National Asthma Education Prevention Program (NAEPP) guidelines were too old to address our 2009 study and the 2020 targeted update did not address anti-acid therapy for asthma.

So the NIH asthma guidelines still don’t mention the futility of anti-acid therapy for asthma control but....anti-acid therapies do not improve asthma control.

Another pharmacy pearl......Beta blockers. Carvedilol has been generic for a few years now and is a popular non-selective (β1 and β2) beta blocker.
Key Objectives:
• Revisit a couple aspects of asthma that have always been true
  • Don’t use anti-acid therapy thinking it will help asthma
  • Remember that non-selective beta blockers can be a problem, including ophthalmic preps.

Something else that has always been true: many patients do not use their inhaler devices properly....
One intervention with durable benefits...delivery device teaching

NAEPP, pg 128

Spacers always recommended for pMDIs to both increase lung distribution and reduce systemic adverse effects

**How to Get Started Using Your PULMICORT FLEXHALER® (budesonide inhalation powder, 90 mcg & 180 mcg)**

**Priming Your PULMICORT FLEXHALER**

Before you use a new PULMICORT FLEXHALER for the first time, you must prime it.

**Loading a Dose**

1. Hold your PULMICORT FLEXHALER upright as described above. With your other hand, twist the white cover and lift it off (see Figure 2).
2. Continue to hold your PULMICORT FLEXHALER upright to be sure that the right dose of medicine is loaded.
3. Use your other hand to hold the inhaler in the middle. Do not hold the mouthpiece when you hold the inhaler.
4. Twist the brown grip fully in one direction as far as it will go. Twist it fully back again in the other direction as far as it will go (it does not matter which way you turn it first) (see Figure 3).
   - You will hear a “click” during one of the twisting movements (see Figure 4).
   - PULMICORT FLEXHALER will only give one dose at a time, no matter how often you click the brown grip, but the dose indicator will continue to move (advance). This means that if you continue to move the brown grip, it is possible for the indicator to show fewer doses or zero doses even if more doses are left in the inhaler.
   - Do not shake the inhaler after loading it.

**Steps for Using Your Inhaler**

**Getting ready**

1. Take off the cap and shake the inhaler.
2. Breathe out all the way.
3. Hold your inhaler the way your doctor said (A, B, or C below).

**Breathe in slowly**

4. As you start breathing in slowly through your mouth, press down on the inhaler one time. (if you use a holding chamber, first press down on the inhaler. Within 5 seconds, begin to breathe in slowly.)
5. Keep breathing in slowly, as deeply as you can.
6. Hold your breath as you count to 10 slowly, if you can.
7. For inhaled quick-relief medicine (beta-agonists), wait about 15-30 seconds between puffs. There is no need to wait between puffs for other medicines.

**Hold your breath**

A. Hold inhaler 1 to 2 inches in front of your mouth (about the width of two fingers).
B. Use a spacer/holding chamber. These come in many shapes and can be useful to any patient.
C. Put the inhaler in your mouth. Do not use for steroids.
Key Objectives:

• Revisit a couple aspects of asthma that have always been true
  • Don’t use anti-acid therapy thinking it will help asthma
  • Remember that non-selective beta blockers can be a problem, including ophthalmic preps.
  • Watching a patient use their inhaler device can be very instructive

PFTs probably underutilized.....
Even though we are all comfortable making a clinical diagnosis of asthma, I’m still a fan of PFTs in many patients, especially if the diagnosis is not a clinical slam dunk (patient is a little older, no real obvious history of triggers and/or no seasonality to their disease).

About 10% of abnormal PFTs at OHSU are NOT an obstructive pattern.

The airways are fine and ‘restriction’ is to lung expansion vs. bronchial air flow. Amiodarone is classic example of drug-induced restrictive disease.
Key Objectives:

• Revisit a couple aspects of asthma that have always been true
  • Don’t use anti-acid therapy thinking it will help asthma
  • Remember that non-selective beta blockers can be a problem, including ophthalmic preps.
  • Watching a patient use their inhaler device can be very instructive
  • PFTs are great to obtain if there is any clinical question about the disease diagnosis
I’m always reminded when I talk to patients in the hospital with an asthma exacerbation that subjective symptoms are very discordant from objective measures of lung function...
Daily symptoms of asthma do not correlate well with lung volume findings:

Exacerbations come from down here....

\[ r=0.143, p=0.2 \]
New guidelines for better asthma control

Last week, the US National Asthma Education and Prevention Program issued the first comprehensive update of its clinical guidelines for the diagnosis and management of asthma in a decade. The 500-page document is rigorous and evidence-based. It integrates the latest scientific evidence into the four essential components of asthma care: assessment and monitoring, patients’ education, control of factors contributing to asthma severity, and drug treatment.

There is increasing evidence that asthma is a heterogeneous disease and is especially a child-guideline. Despite this, the treatment benefits far outweigh the risks. Additionally, there are now separate treatment recommendations for children aged 0–4 years, 5–11 years, and 12 years and older. The 5–11 year age group was added (earlier guidelines combined this group with adults) because of new evidence suggesting that children might respond differently from adults to asthma drugs.

The guidelines place a strong emphasis on monitoring asthma control. The new approach focuses on two related yet distinct aspects of the disease: the level of daily impairment that a patient is experiencing and the patient’s future risk for exacerbations, loss of lung function, and drug side-effects. This new distinction is important because it addresses the fact that some patients still be

The asthma guidelines place a lot of emphasis on monitoring lung volumes at home due to the disconnect between symptoms and volume....

\[ \text{The Lancet} \]
Key Objectives:
• Revisit a couple aspects of asthma that have always been true
  • Don’t use anti-acid therapy thinking it will help asthma
  • Remember that non-selective beta blockers can be a problem, including ophthalmic preps.
  • Watching a patient use their inhaler device can be very instructive
  • PFTs are great to obtain if there is any clinical question about the disease diagnosis
• Home peak flow monitoring for patients with a history of severe exacerbations still a very good idea
So a number of things about asthma management have NOT changed but “Treatment Approach” is no longer one of them.

NAEPP page 343

GINA 2019 guidelines say first line: formoterol+ICS

Symbicort is with budesonide

Dulera is with mometasone

“SMART” approach: Single Maintenance and Reliever Therapy
Who are the GINA guidelines authors?

“In 1993, NIH/NHLBI convened the NAEPP work group......”

“...This was followed by the establishment of GINA, a network of individuals, organizations and public health officials.....to provide a mechanism to translate scientific evidence into improved asthma care....The GINA assembly was subsequently initiated, as an ad hoc group of dedicated asthma care experts from many countries....”

There are 15 members of their scientific writing Board and 12 members of the Board of Directors (many overlap)
Here are financial disclosure statements for first 4 GINA co-authors. The total COI document is 25 pages long.
How were financial COI handled as “GINA” authors voted that everyone should use $300-400 Dulera or Symbicort?

Compared to NIH NAEPP guideline, less clear how GINA guidelines handle financial COI. Conflicted members of the 15-person scientific writing board appear to retain ability to vote on pathway updates....
So, “GINA” authors say no more prn SABA for any asthmatic....

NAEPP page 343

GINA 2019 guidelines say first line: formoterol+ICS

Symbicort is with budesonide

Dulera is with mometasone

“SMART” approach: Single Maintenance and Reliever Therapy
% Change in FEV1 in first hour

Onset of albuterol: < 2 min
Effective clinical duration: 4 hours
% Change in FEV1 over 12 hours

At the 12th hour after a LABA dose, the patient has about 50% of their peak effect.
Why the “SMART” approach from GINA?

1. Asthmatics that are pretty healthy often only use their “reliever” because that’s the one that makes them acutely feel better....but that’s a problem

2. The inflammation in asthma is very amenable to corticosteroid therapy and missed use of ICS (inhaled corticosteroid) misses the opportunity to control the disease
Why the “SMART” approach?

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Controversies settled in asthma: Scheduled, daily use of SABA?: NO - NAEPP 2007 guidelines, page 236

**KEY POINTS: SAFETY OF INHALED SHORT-ACTING BETA$_2$-AGONISTS**

- SABAs are the most effective medication for relieving acute bronchospasm (Evidence A).
- Increasing use of SABA treatment or using SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control of asthma and the need for initiating or intensifying anti-inflammatory therapy (Evidence C).
- Regularly scheduled, daily, chronic use of SABA is not recommended (Evidence A).

**Adverse effects:**

These drugs are related to adrenaline (epinephrine) and are mild stimulants but most importantly, overuse can mask progressing, underlying disease.
LABA (long-acting beta agonist): Manufacturer of Salmeterol did a trial of that drug as the “controller” for mild persistent asthma and it failed.

FDA put a black box warning on LABA for asthma without a controller.

**WARNING: ASTHMA-RELATED DEATH**
See full prescribing information for complete boxed warning.

- Long-acting beta$_2$-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. A U.S. trial showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 out of 13,179 subjects on placebo). Currently available data are inadequate.
Controversies in Asthma: LABA not harmful when added to a controller

*Controversies in Asthma: LABA not harmful when added to a controller*

![Graph showing LABA risk differences](image)

*Asthma composite risk: death from asthma, intubation, hospitalization*

**LABAs:** Salmeterol and formoterol are bronchodilators that have a duration of bronchodilation of at least 12 hours after a single dose.

- **LABAs are not to be used as monotherapy for long-term control of asthma (Evidence A).**
- **LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma (step 3 care or higher in children ≥5 years of age and adults) (Evidence A for ≥12 years of age, Evidence B for 5–11 years of age).**

*NAEPP, page 213*
Why the “SMART” approach?

1. Asthmatics that are pretty healthy often only use their “reliever” because that’s the one that makes them acutely feel better….but that’s a problem

2. The inflammation in asthma is very amenable to corticosteroid therapy and missed use of ICS (inhaled corticosteroid) misses the opportunity to control the disease
Editorials

Eat Dirt — The Hygiene Hypothesis and Allergic Diseases

There has been an epidemic of both autoimmune diseases (in which the immune response is dominated by type 1 helper T [Th1] cells, such as type 1 diabetes, Crohn’s disease, and multiple sclerosis) and allergic diseases (in which the immune response is dominated by type 2 helper T [Th2] cells, such as asthma, allergic rhinitis, and atopic dermatitis), as documented in the article by Bach in this issue of the Journal.¹ The occurrence of these diseases is higher
The inflammation in asthma is different from COPD and more amenable to steroid therapy....
Why control: Poorly controlled asthmatics with moderate-severe disease lose lung volume faster than smokers

*NEJM 1998;339:1194-200*

**A 15-YEAR FOLLOW-UP STUDY OF VENTILATORY FUNCTION IN ADULTS WITH ASTHMA**

PETER LANGE, M.D., PH.D., JAN PARNER, JØRGEN VESTBO, M.D., PH.D., PETER SCHNOHR, M.D., AND GORM JENSEN, M.D., PH.D.
“Controllers” help bend the disease curve and slow the rate of loss of lung function

Xolair available (in theory)

Corticosteroids act here to reduce inflammatory response (oral agents usually only used acutely for exacerbations due to long-term side effects)

Zafirlukast (Accolate) Montelukast (Singulair) (used chronically but a fraction as potent as steroids in terms of antiinflammatory response)

Allergen + IgE

Mast cell contents
- Histamine
- Recruit mediators (IL’s, lymphokines, eosinophils)

Mast cell membrane rupture (phospholipid release)

Arachidonic acid

Lipoxygenase
- Leukotrienes
  - LTD4
  - LTE4

Cyclooxygenase
- Prostaglandins
  - PGE
  - prostacyclin
  - thromboxane

“Receptors”

Zafirlukast (Accolate) Montelukast (Singulair)
In terms of comparative efficacy of controllers for asthma:

Efficacy of Inhaled Corticosteroids as Compared to Other Long-Term Control Medications as Monotherapy

The Expert Panel concludes that studies demonstrate that ICSs improve asthma control more effectively in both children and adults than LTRAs or any other single long-term control medication (Evidence A).

NAEPP page 217
Key Objectives:
• Revisit a couple aspects of asthma that have always been true
  • Important concepts to the “SMART” study design; 1. using relievers without a controller for asthma increases the risk of asthma-related death and 2. Unlike with COPD, inhaled steroids are generally very effective at treating the eosinophil-mediated inflammation in asthma
Therapeutic strategies. Optimizing asthma control: Adults/adolescents

**FIGURE 4–5. STEPWISE APPROACH FOR MANAGING ASTHMA IN YOUTHS ≥12 YEARS OF AGE AND ADULTS**

**Step 1**
- **Preferred:** Low-dose ICS
- **Alternative:** Cromolyn, LTRA, Nedocromil, or Theophylline

**Step 2**
- **Preferred:** Low-dose ICS + LABA OR Medium-dose ICS
- **Alternative:** Low-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 3**
- **Preferred:** Medium-dose ICS + LABA
- **Alternative:** Medium-dose ICS + either LTRA, Theophylline, or Zileuton

**Step 4**
- **Preferred:** High-dose ICS + LABA AND Consider Omalizumab for patients who have allergies

**Step 5**
- **Preferred:** High-dose ICS + LABA + oral corticosteroid AND Consider Omalizumab for patients who have allergies

**Step 6**
- Assess control

*Step up if needed (first, check adherence, environmental control, and comorbid conditions)*

*Step down if possible (and asthma is well controlled at least 3 months)*

- Each step: Patient education, environmental control, and management of comorbidities.
- Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

**Quick-Relief Medication for All Patients**
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

“GINA” says no more

NAEPP page 343
GINA guidelines, 2019:

“SMART” approach: Single Maintenance and Reliever Therapy
SECTION IV: Recommendations for the Use of Intermittent Inhaled Corticosteroids in the Treatment of Asthma
NIH NAEPP guidelines in 2020 retained the prn SABA approach for intermittent asthma patients (2 or fewer uses of reliever per week).....
Why did NAEPP in 2020 **NOT** endorse the “S.M.A.R.T” approach to intermittent asthma?

1. Dulera or Symbicort are expensive ($300-400 each) and

2. The trials in 2018 which led to the GINA update in 2019 studied patients who mostly had persistent asthma and therefore should have already been on a controller. Not surprisingly, low dose ICS + formoterol beat prn albuterol GINA step 2 means symptoms “at least” twice monthly but less than daily.

But, on average.......
The “SMART” trials overwhelmingly studied patients with persistent asthma who already qualified for a daily controller per the 2007 NIH EPR 3 guidelines.

What did they find in that persistent asthma population?
In the trials, exacerbation rates are the same with scheduled low dose ICS or prn ICS+formoterol but.....
In the trials, exacerbation rates are the same with scheduled low dose ICS or prn ICS+formoterol but.....

But, overall, # weeks of controlled asthma were actually better with scheduled controller
Key Objectives:

• Revisit a couple aspects of asthma that continue to be true
• Consider the discordance of recent guideline updates which no longer completely agree
  • So, in the SMART-designed trials of mild asthma, prn formoterol+ICS beats prn SABA in patients with mild persistent asthma who need a controller but it does not beat scheduled ICS and scheduled ICS showed more days of asthma control
So again, NAEPP in 2020 didn’t change their recommendation for Intermittent asthma patients....

Just a reminder WHO those “intermittent” patients are....

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Youths ≥12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td>Persistent</td>
</tr>
<tr>
<td>Normal FEV₁/FVC</td>
<td>Intermittent</td>
</tr>
<tr>
<td>8–19 yr</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>20–39 yr</td>
<td>≤2x/month</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>60–80 yr</td>
<td>None</td>
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<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
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<tr>
<td>FEV₁/FVC normal</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC normal</td>
<td></td>
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<tr>
<td>Normal FEV₁ between exacerbations</td>
<td></td>
</tr>
<tr>
<td>FEV₁ &gt;80% predicted</td>
<td></td>
</tr>
<tr>
<td>FEV₁/FVC normal</td>
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<tr>
<td>FEV₁/FVC normal</td>
<td></td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year (see note)</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
</tr>
</tbody>
</table>
| Relative annual risk of exacerbations may be related to FEV₁ | Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.
Summary of the “SMART” approach to asthma care:

1. Not yet proven if necessary for truly “intermittent” asthma patients and prn SABA still endorsed by NIH NAEPP 2020 update

2. The S.M.A.R.T. approach must use a formoterol-containing MDI and they are expensive (check insurance)

3. The S.M.A.R.T. approach is clearly superior to SABA alone in persistent asthma but no better than scheduled ICS with a separate reliever in those patients

4. For patients who cannot manage multiple inhalers and are only using their “reliever,” a S.M.A.R.T. approach can be an attractive option (if affordable) to ensure some use of ICS
Thank you