GINA 2020:
Updates from the Global Initiatives for Asthma

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FAMILY MEDICINE UPDATE 2021

LEARNING OBJECTIVES

1. Review the diagnostic criteria and evaluation of patients with asthma.


3. Review common medications used for acute and chronic management of asthma.

Other famous GINAs:
Not sure their thoughts on ICS-LABAs

GINA ESQUI
*MU FCM residency coordinator
*Local celebrity, surrogate mother to many residents
*Doesn’t cry with making schedules

GINA SILVEY
*Residency coordinator
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*Doesn’t cry playing baseball
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ASTHMA GUIDELINE UPDATES

- GINA: Global Initiative for Asthma updated recommendations in 2019 and 2020
- NIH and National Heart, Lung, and Blood Institute updated recommendations in 2020
- Similarities and differences between the two organizations approaches/recommendations

ASTHMA DEFINITION

- “Heterogenous disease characterized by chronic airway inflammation”
- Defined by symptoms which vary over time and in intensity
  - Wheeze
  - Shortness of breath
  - Chest tightness
  - Cough
  - Variable expiratory airflow limitations which may become persistent
- Symptoms often brought on by triggers and relieved by bronchodilator medications
- Bronchial hyperresponsiveness in reaction to stimuli

ASTHMA PATHOPHYSIOLOGY

- Airway biopsies show similar inflammatory process as with allergic response in nasal mucosa and skin
  - Supports belief of mast cell activation playing a role in asthma
  - Eosinophil accumulation
- Airflow obstruction results from
  - Contraction of smooth muscle in airway
  - Thickening of airway due to edema
  - Collection of mucus or cellular debris
  - Airway remodeling
- Airway remodeling may lead to irreversible obstruction over time
Current Asthma Prevalence: United States, 2001-2017

About 25 million (8% of the U.S. population) had asthma in 2017, an increase from 20 million, or 7.3% who had asthma in 2001.


Blacks are more likely to have asthma than both whites and Hispanics. Percent of current asthma increased for whites, blacks, and Hispanics from 2001 to 2017.

Current Asthma Prevalence by Age Group, Sex, Race and Ethnicity, Poverty Status, Geographic Region, and Place of Residence: United States, 2017

Females, blacks, and Puerto Ricans are more likely to have asthma. People with lower annual household income were more likely to have asthma. Asthma did not differ by age group, region, or Metropolitan Statistical Area (MSA).
Child and Adult Current Asthma Prevalence by Age and Sex: United States, 2017

Among children 0-4 years, males had a higher percent of asthma and among adults 25 years and older, was higher for women than men.

Asthma Deaths: United States, 2001–2017

The rate of asthma deaths declined from 15.0 per million population in 2001 to 11.2 deaths per million population in 2008. Rates gradually peaked between 2011 and 2014 but not significant.

DIAGNOSIS

Evaluation focuses on use pulmonary function testing (PFTs)

Consistent use of pulmonary function testing reduces the risk of both UNDER-diagnosis and OVER-diagnosis.

May also consider:
- CXR
- Allergy testing
- Focused lab evaluation
- CBC
- Further based on evaluation of differential
DIAGNOSIS - PFTs

• Office-based spirometry to measure FEV1 and FVC
  - Determine baseline airflow obstruction (reduced FEV1/FVC)
  - Determine severity of obstruction
  - Evaluate for other causes of dyspnea - restrictive lung disease

• Full PFTs will also measure lung volumes and gas exchange
  - Can clarify if restrictive or mixed restrictive/obstructive

• Peak Flow device: monitor as opposed to diagnosis
  - Abnormal results can be suggestive but is not specific
  - Peak flow responding to SABA supportive

Langan, AAFP, 2020

Normal PFTs but still suspicious for asthma?
ASTHMA - DIAGNOSIS

Consider bronchoprovocation testing if spirometry normal (normal ratio, no bronchodilator change)

Also consider:

- Repeat spirometry at future visit when symptomatic
- Regular, routine home Peak Flow monitoring
  - Measure AM and PM, with and without symptoms, after bronchodilator
ASTHMA – TREATMENT GOALS

• Reduce symptom burden
• Prevent exacerbations
• Maximize lung function
• Individualize treatment based on frequency and intensity of symptoms AND risk of exacerbations
• Education, communication and regular follow-up

The GINA report is not a guideline, but an integrated evidence-based strategy focusing on translation into clinical practice.
Recommendations are framed, not as answers to isolated PICOT questions, but as part of an integrated strategy, in relation to:

§ The GINA goals of preventing asthma deaths and exacerbations, as well as improving symptom control
§ Current understanding of underlying disease processes
§ Human behavior (of health professionals and patients/carers)
§ Implementation in clinical practice
§ Global variation in populations, health systems and medication access
Patients with apparently mild asthma are at risk of serious adverse events:
- 30–37% of adults with acute asthma
- 16% of patients with near-fatal asthma
- 15–20% of adults dying of asthma

Exacerbation triggers are variable (viruses, pollens, pollution, poor adherence)

Inhaled SABA has been first-line treatment for asthma for 50 years:
- This dates from an era when asthma was thought to be a disease of bronchoconstriction
- Patient satisfaction with, and reliance on, SABA treatment is reinforced by its rapid relief of symptoms, its prominence in ED and hospital management of exacerbations, and low cost
- Patients commonly believe that “My reliever gives me control over my asthma”, so they often don’t see the need for additional treatment

Regular or frequent use of SABA is associated with adverse effects:
- β2-receptor desensitization, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response
- Increased allergic response, and increased eosinophilic airway inflammation
- Higher use of SABA is associated with adverse clinical outcomes:
  - Dispensing of ≥3 canisters per year (average 1.7 puffs/day) is associated with higher risk of emergency department presentations
  - Dispensing of ≥12 canisters per year is associated with higher risk of death

Since 2007, GINA has been actively seeking interventions for mild asthma:
- to reduce the risk of asthma-related exacerbations and death
- to provide consistent messaging about the goals of asthma treatment, including prevention of exacerbations, across the spectrum of asthma severity
- to avoid establishing patient reliance on SABA early in the course of the disease
- GINA emphasized poor adherence as a modifiable risk factor for exacerbations
  - When the reliever is SABA, poor adherence with maintenance controller exposes the patient to risks of SABA-only treatment
  - GINA members repeatedly sought funding for RCTs of as-needed ICS-formoterol for risk reduction in mild asthma
  - Eventually culminated in 2014 with the initiation of the SYGMA studies, published in 2018

The 12-year history behind changes in GINA 2019:
- The risks of ‘mild’ asthma
- The risks of SABA-only treatment
- Background to changes in 2019
In the meantime, GINA challenged conventional criteria for initiation of ICS
- During preparation for 2014 GINA revision, we identified no evidence for the
  recommendation to withhold ICS until symptoms were more than twice weekly
- This was investigated in data from the START study (Pauwels, Lancet 2003). A post-
  hoc analysis found that ICS halved the risk of serious exacerbations even in patients
  with symptoms 0-1 days a week at entry (Reddel, Lancet 2017)
- GINA found no evidence to support a Step 1 SABA-only recommendation
  - The lack of evidence for SABA-only treatment contrasted with the strong evidence for
    safety, efficacy and effectiveness of treatments recommended in Steps 2-5
  - In 2014, as an interim safety measure, GINA restricted SABA-only treatment to
    patients with symptoms less than twice a month and no risk factors for exacerbations
- 2018: Review of evidence for mild asthma, including SYGMA studies
  - A careful review of GINA conflict of interest processes was undertaken first
GINA 2019 – landmark changes in asthma management

- For safety, GINA no longer recommends SABA-only treatment for Step 1
  - This decision was based on evidence that SABA-only treatment increases the risk of severe exacerbations, and that adding any ICS significantly reduces the risk
- GINA now recommends that all adults and adolescents with asthma should receive ICS-containing controller treatment, to reduce the risk of serious exacerbations
  - The ICS can be delivered by regular daily treatment or, in mild asthma, by as-needed low dose ICS-formoterol
- This is a population-level risk reduction strategy
  - Other examples: statins, anti-hypertensives
  - Individual patients may not necessarily experience (or be aware of) short-term clinical benefit
  - The aim is to reduce the probability of serious adverse outcomes at a population level

SYGMA 1: Symbicort Given as needed in Mild Asthma

- Double-blind RCT, 52 weeks enrolled patients aged 12 and older with clinical diagnosis of asthma for at least 6 months based on GINA criteria
- Enrolled 3849 patients, eligible if needing Step 2 treatment (uncontrolled with SABA PRN or well-controlled with ICS+SABA prn or LTRA+SABA prn)
- Compared:
  - BID placebo + terbutaline (0.5mg) PRN
  - BID placebo + budesonide-formoterol (200 mcg budesonide with 6mcg formoterol) PRN
  - BID budesonide (200mcg) plus terbutaline PRN
- Sponsored by AstraZeneca

- Primary outcome compared budesonide-formoterol PRN compared to prn terbutaline based on:
  - Electronically recorded weeks with well-controlled asthma based on electronic diary data for asthma symptom scores, nighttime awakenings, morning peak flows, and use of inhaled/systemic steroids
- Secondary outcome compared budesonide-formoterol for PRN vs budesonide maintenance
RESULTS

Primary outcome:
- Electronically recorded results with well-controlled asthma per patient
  - 34.4% in budesonide-formoterol PRN
  - 31.1% in Terbutaline PRN
  - OR 1.14 (1.00–1.30, p=0.046)
  - Odds of having well-controlled asthma during the 52 weeks was 14% higher with PRN budesonide-formoterol

Secondary outcome:
- Budesonide-formoterol PRN inferior to budesonide maintenance therapy for weeks with well-controlled asthma
  - 34.4% vs 44.4%, OR 0.64 (0.57–0.73)
- Accumulative steroid dose lower in PRN budesonide-formoterol

Severe exacerbation: worsening asthma leading to use of systemic steroids ≥ 3 days, inpatient hospitalization or ED visit leading to use of systemic steroids
RESULTS

- Budesonide-formoterol PRN non-inferior to Budesonide maintenance with PRN terbutaline
- Rate of severe exacerbations: 0.11 vs 0.12

Secondary Outcomes:
- No difference in adherence
- Higher total inhaled steroid dose in maintenance arm.
- No difference in mean change of salbutamol free days.
- Change in baseline of FEV1 with inhaled steroid was less in budesonide-formoterol PRN.
- ACQ-5 score decreased less in budesonide-formoterol PRN
- No difference in adverse events
Additional supporting evidence

- Two additional RCTs of as-needed low dose budesonide-formoterol in mild asthma
  - 12-month studies, open-label, no twice-daily placebo, i.e. the way it would be used in real life
  - Novel START (Beasley et al, NEJM 2019, n=892) and PRACTICAL (Hardy et al, Lancet 2019, n=1189)
  - Significant reduction in severe exacerbations vs SABA alone, and vs maintenance ICS, with small or no difference in symptom control, and lower average ICS dose
  - Patients in RCTs of this regimen in mild asthma now total n=9,865

- Both of these studies included inflammatory markers
  - FeNO was significantly reduced by as-needed ICS-formoterol (with average 3-5 doses per week)
  - Reduction in risk of severe exacerbations with as-needed ICS-formoterol was independent of baseline characteristics, including blood eosinophils and exhaled nitric oxide

- An additional RCT of taking ICS whenever SABA is taken (separate inhalers)
  - ASIST, in African-American children 6-17 years with mild asthma, compared with physician-adjusted treatment (Sumino et al, JACI in Pract 2019, n=206)

Results

- Primary outcome: exacerbation rate
  - Budesonide-formoterol PRN vs. albuterol PRN: 0.195 vs 0.400, RR 0.49 (0.33-0.72)
  - Budesonide-formoterol PRN vs. budesonide maintenance: 0.195 vs 0.175, RR 1.12 (0.70-1.79)

- Severe exacerbation: prescription of steroid for 3 days or hospitalization or ED visit requiring systemic steroids
RESULTS

• Enrollee at baseline:
  - More women in budesonide groups
  - More severe exacerbations in past 12 months in albuterol-only group

• Enrollees were less severe at baseline compared to SYGMA

• Authors note these findings support SYGMA 1 and 2 trials and ultimately support GINA 2019 updates

Open-label RCT, adults aged (18-75) with self-reported asthma diagnosis using SABA for symptom relief with or without maintenance low to moderate doses of inhaled steroids in past 12 weeks (mild to moderate asthma)

- 55% female, average age 43, 79% European ethnicity

- Assigned 890 participants:
  - Budesonide-formoterol (200mcg-6mcg) PRN
  - Budesonide (200mcg) BID plus terbutaline (250mcg) PRN

- Primary outcome: number of severe exacerbations per patient per year defined as use of systemic steroids for at least 3 days or admission to hospital or ED visit requiring systemic steroids

- Funded by AstraZeneca

PRACTICAL: PeRsonalized Asthma Combination Therapy with inhaled Corticosteroid And fast-onset long-acting Beta agonist

RESULTS

• Rate of asthma exacerbations budesonide-formoterol PRN vs budesonide maintenance
  - 0.119 vs 0.172, RR 0.69 (CI 0.48-1.00, P=0.049)

• Small overall difference but supports use of less regular steroid

• Enrolled patients with mild-to-moderate asthma

• Complements Novel START study
WHERE TO START WITH MEDICATION DOSING?
WHAT ABOUT YOUNGER CHILDREN?
Low, medium and high doses of different ICS

- NOT a table of equivalence
  - Suggested total daily doses for 'low', 'medium' and 'high' dose treatment options
  - Based on available studies (very few) and product information
  - Does NOT imply potency equivalence
- Doses may be country-specific depending on local availability, regulatory labeling and clinical guidelines
- Clinical relevance
  - Low dose ICS provides most of the clinical benefit of ICS for most patients with asthma
  - However, ICS responsiveness varies between patients, so some patients may need medium dose ICS if their asthma is uncontrolled despite good adherence and correct technique
  - High dose ICS (in combination with LABA or separately) is needed by very few patients
    - Its long-term use is associated with an increased risk of local and systemic side-effects, which must be balanced against the potential benefits
### Low, medium and high ICS doses: adults/adolescents

<table>
<thead>
<tr>
<th>Inhaler corticosteroid</th>
<th>Total daily ICS dose (μg)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (MDI, standard particle, HFA)</td>
<td>250–300</td>
<td>200–250</td>
<td>&gt;250</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (MDI, extrafine particle, HFA)</td>
<td>125–150</td>
<td>100–125</td>
<td>&gt;125</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Budesonide (MDI)</td>
<td>200–250</td>
<td>150–200</td>
<td>&gt;150</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Ciclesonide (pMDI, extrafine particle, HFA)</td>
<td>80–100</td>
<td>60–80</td>
<td>&gt;60</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
<td>100–200</td>
<td>75–150</td>
<td>&gt;75</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Fluticasone propionate (MDI, standard particle, HFA)</td>
<td>100–200</td>
<td>75–150</td>
<td>&gt;75</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Mometasone furoate (DPI)</td>
<td>125–250</td>
<td>100–200</td>
<td>&gt;100</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Mometasone furoate (MDI, standard particle, HFA)</td>
<td>250–500</td>
<td>200–500</td>
<td>&gt;200</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>

This is NOT a table of equivalence. These are suggested total daily doses for the 'low', 'medium' and 'high' dose treatment options with different ICS.

DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC); * see product information

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### Low, medium and high ICS doses: children 6–11 years

<table>
<thead>
<tr>
<th>Inhaler corticosteroid</th>
<th>Total daily ICS dose (μg)</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (MDI, standard particle, HFA)</td>
<td>150–225</td>
<td>125–175</td>
<td>&gt;125</td>
<td>&gt;225</td>
</tr>
<tr>
<td>Beclomethasone dipropionate (MDI, extrafine particle, HFA)</td>
<td>75–115</td>
<td>60–100</td>
<td>&gt;60</td>
<td>&gt;115</td>
</tr>
<tr>
<td>Budesonide (MDI)</td>
<td>180–250</td>
<td>150–200</td>
<td>&gt;150</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Ciclesonide (pMDI, extrafine particle, HFA)</td>
<td>80–120</td>
<td>60–80</td>
<td>&gt;60</td>
<td>&gt;120</td>
</tr>
<tr>
<td>Fluticasone furoate (DPI)</td>
<td>100–200</td>
<td>75–150</td>
<td>&gt;75</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Fluticasone propionate (MDI, standard particle, HFA)</td>
<td>100–200</td>
<td>75–150</td>
<td>&gt;75</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Mometasone furoate (DPI)</td>
<td>150–250</td>
<td>100–200</td>
<td>&gt;100</td>
<td>&gt;250</td>
</tr>
<tr>
<td>Mometasone furoate (MDI, standard particle, HFA)</td>
<td>250–500</td>
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DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; pMDI: pressurized metered dose inhaler (non-CFC); * see product information

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### Box 4.8: Personalised management of asthma in children 5 years and younger

**Children 5 years and younger**

Personalised asthma management:
- Medication management
- Monitoring
- Education/ empowerment
- Written action plan
- Self-management

**Step 1. Assessment**

- Identify child and family needs
- Assess asthma severity
- Check for co-morbidities
- Family history

**Step 2. Plan**

- Set measurable goals
- Identify triggers
- Monitor progress

**Step 3. Implement**

- Adjust medication
- Anticipate future triggers
- Educate family

**Step 4. Review**

- Monitor progress
- Adjust treatment
- Reassess asthma severity
- Update written action plan
Low, medium and high ICS doses: children 5 years and younger

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Low total daily dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDP (AER, standard particle, HFA)</td>
<td>108 mcg (ages 5 years and older)</td>
</tr>
<tr>
<td>BDP (AER, extética particle, HFA)</td>
<td>50 mcg (ages 5 years and older)</td>
</tr>
<tr>
<td>Budesonide inhaler</td>
<td>900 mcg (ages 1 year and older)</td>
</tr>
<tr>
<td>Budesonide pMDI</td>
<td>900 mcg (ages 1 year and older)</td>
</tr>
<tr>
<td>Fluticasone propionate (AER, standard particle, HFA)</td>
<td>900 mcg (ages 1 year and older)</td>
</tr>
<tr>
<td>Fluticasone propionate (AER, extética particle, HFA)</td>
<td>Not sufficiently studied in children 5 years and younger</td>
</tr>
<tr>
<td>Mometasone furoate (AER, standard particle, HFA)</td>
<td>Not sufficiently studied in children 5 years and younger</td>
</tr>
<tr>
<td>Mometasone furoate (AER, extética particle, HFA)</td>
<td>Not sufficiently studied in children 5 years and younger</td>
</tr>
<tr>
<td>Fluticasone pMDI</td>
<td>Not sufficiently studied in children 5 years and younger</td>
</tr>
</tbody>
</table>

This is NOT a table of equivalence. These are suggested total daily doses for the low dose treatment options with different ICS.

- As-needed low dose budesonide-formoterol
  - Prescribed in maintenance and reliever therapy (Steps 3–5), or as-needed only (Steps 1–2), or within an asthma action plan
  - From product information, the maximum recommended total in one day is 72 mcg formoterol (12 inhalations of budesonide-formoterol Turbuhaler 200/6 mcg)

- As-needed low dose beclometasone-formoterol
  - Prescribed in maintenance and reliever therapy (Steps 3–5), or within an asthma action plan
  - From product information, the maximum recommended total in one day is 48 mcg formoterol (6 inhalations of beclometasone-formoterol pMDI100/6 mcg)

12+ years

- Confirmation of diagnosis
- Symptom control and reduction

Need for reassessment and monitor of interventions
n
FDA boxed warning in March 2020 about risk of serious neuropsychiatric events, including suicidality, with montelukast
- Includes suicidality in adults and adolescents
- Nightmares and behavioral problems in children

Before prescribing montelukast, health professionals should consider its benefits and risks, and patients should be counseled about the risk of neuropsychiatric events
GINA 2020 on Asthma and COPD Overlap

Patients with features of asthma and COPD

- Also called ‘asthma-COPD overlap’ or ‘asthma+COPD’
  - NOT a single disease, but a descriptive label for patients commonly seen in clinical practice
  - Asthma and COPD are heterogeneous and overlapping conditions
    - The definitions of asthma and COPD are not mutually exclusive
    - Each includes several phenotypes that are likely to have different underlying mechanisms
    - There is increasing interest in the potential for precision treatment

- However, the labels ‘asthma’ and ‘COPD’ are still clinically important, as evidence supports safety-based differences in treatment 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 diagnoses of 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 2018)
  - High-dose ICS may be needed for severe asthma, but should not be used in COPD (risk of pneumonia)

- Chapter 5 has been rewritten for clinical utility, focusing on clinical recognition and safe initial treatment

Patients with features of asthma and COPD

- Clinical pattern: adults with chronic respiratory symptoms (cough, shortness of breath, wheeze)
  - History
    - Suggests wheezing or coughing
      - History of asthma
      - History of chronic bronchitis
    - Present for at least 2 years
      - Persistent or episodic
    - History of symptoms worse in cold weather
    - History of symptoms worse at night
  - Examination
    - Auscultation: wheezing or rhonchi
    - Auscultation: wheezing or rhonchi
  - Labs: spirometry showing airway obstruction
    - FEV1/FVC < 70%
    - Airway hyperresponsiveness
- Features of both asthma & COPD
  - Persistent cough and sputum
  - History of smoking
  - history of chronic bronchitis
  - History of exacerbations
  - History of symptoms worse in cold weather
  - History of symptoms worse at night
  - History of symptoms worse after exercise
- Levels To Be COPD (TREAT AS COPD)
  - History of smoking
  - Chronic bronchitis
  - Chronic obstructive pulmonary disease

- Management
  - Treatment of exacerbations
  - Treatment of COPD
  - Treatment of COPD
  - Treatment of exacerbations
  - Treatment of exacerbations

- GINA Pocket Guide for ESMT: Access for Expert-Sense of Anticipation or Marginal Response
Questions?
RESOURCES

- Asthma Management Guidelines: A report from the national asthma education and prevention program coordinating committee expert panel. NEJM 2019; 381: 1740-1765
- CDC Asthma Surveillance data. https://www.cdc.gov/asthma/asthmadata.htm