Asthma 2019: What's New and Practical for All?  
... a peek at GINA...  

Randall Brown, MD MPH AE-C  
Pulmonologist | Pediatrician | Health Educator  
Director, Asthma and COPD Programs  
Center for Managing Chronic Disease  
University of Michigan

Faculty Disclosures
Randall Brown, MD MPH AE-C  
Pulmonologist | Pediatrician | Health Educator  
Director, Asthma & COPD Programs  
Center for Managing Chronic Disease | Health Behavior & Health Education  
School of Public Health | University of Michigan

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Remember this Fuzzy Image?
Through the Fog: August 28, 2007

- President: George W. Bush
- Best Movie: The Departed
- Top Song: Rihanna (featuring Jay-Z)
- Smartphone: iPhone
- Top asthma medication: albuterol
- Still the latest and greatest for 2019/2020?

Global Initiative for Asthma (GINA)
What's new in GINA 2019?

GINA Global Strategy for Asthma Management and Prevention

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About the GINA strategy

- 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
- For new therapies, 2 good quality studies + indication by EMA/FDA are required
  - For existing medications with established safety profile, GINA may sometimes make off-label recommendations for new indications (e.g. macrolides for severe asthma)
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 downregulation, decreased bronchoprotection, rebound hyperresponsiveness, decreased bronchodilator response (Hancox, Respir Med 2000)
- Increased allergic response, and increased eosinophilic airway inflammation (Aldridge, AJRCCM 2000)

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 (Stanford, AAAI 2012)
- Dispensing of ≥12 canisters per year is associated with higher risk of death (Suissa, AJRCCM 1994)

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 (O’Byrne NEJM 2018; Bateman NEJM 2018)
The 12-year history behind changes in GINA 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 a post hoc analysis of START data (Pauwels, Lancet 2003). This found that ICS halved the risk of severe 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 2018 – main treatment figure

- Step 1 treatment is for patients with symptoms twice/month and no risk factors for exacerbations
- Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was preferred

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 symptom-driven or regular low dose ICS-containing controller treatment, to reduce the risk of serious exacerbations
  - This is a population-level risk reduction strategy, e.g. statins, anti-hypertensives
Step 2 – rationale for changes in GINA 2019

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GINA 2018 – main treatment figure

Previously, no controller was recommended for Step 1, i.e. SABA-only treatment was ‘preferred’

Step 1 treatment is for mucus with symptoms twice/month and no risk factors for exacerbations

Off-label; data only with budesonide and formoterol

Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken

As-needed low dose ICS – formoterol

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

As-needed low dose ICS – formoterol

STEP 2
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS – formoterol

STEP 3
Low dose ICS – LABA

STEP 4
Medium dose ICS – LABA

STEP 5
High dose ICS – LABA

Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

Confirmation of diagnosis if necessary

Symptom control & modifiable risk factors (including lung function)

Comorbidities

Inhaler technique & adherence

Patient goals

Asthma medications

Non-pharmacological strategies

Education & skills training

Asthma medications

Proven benefits of ICS

Symptoms

Exacerbations

Side effects

Lung function

Patient satisfaction

GINA 2018: 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

GINA 2018: Box 3 - 5A

Adults & adolescents 12+ years

Personalized asthma management: Assess, Adjust, Review response

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GINA 2018: 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 2 – there are two ‘preferred’ controller options

**Regular low dose ICS with as-needed SABA**

- **Evidence**
  - A large body of evidence from RCTs and observational studies that low dose ICS substantially reduces risks of severe exacerbations, hospitalizations and death, e.g. Suissa, NEJM 2001; Suissa, Thorax 2002; Piawet, Lancet 2002; OBryme, AEROCM 2001
  - Severe exacerbations halved even in patients with symptoms 0-1 days per week (Reddel, Lancet 2017)
  - Improved symptom control and reduced exercise-induced bronchoconstriction
- **Values and preferences**
  - High importance was given to preventing asthma deaths and severe exacerbations
  - However, we were aware that poor adherence is common in mild asthma in the community, and that this would expose patients to the risks of SABA-only treatment

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Step 2 – two ‘preferred’ controller options

**As-needed low dose ICS (formoterol) (off-label: all evidence with budesonide-formoterol)**

- **Evidence**
  - Direct evidence from two large studies of non-inferiority for severe exacerbations vs daily low dose ICS + as-needed SABA (OBryme, NEJM 2018; Bateman, NEJM 2018)
  - Direct evidence from one large study of 64% reduction in severe exacerbations vs SABA-only treatment (OBryme, NEJM 2018)
  - Symptoms reduced; one study showed reduced exercise-induced bronchoconstriction
- **Values and preferences**
  - High importance was given to preventing severe exacerbations, avoiding need for daily ICS in patients with mild or infrequent symptoms, and safety of as-needed ICS-formoterol in maintenance and reliever therapy, with no new safety signals
  - Lower importance given to small non-cumulative differences in symptom control (ACQ-5 difference 0.15 vs MCID 0.5) and lung function compared with daily ICS
  - Makes use of normal patient behavior (seeking symptom relief) to deliver controller
Low dose ICS taken whenever SABA taken (off-label, separate or combination inhalers)

Evidence
- Two RCTs showed reduced exacerbations compared with SABA-only treatment
  - TREXIA, in children/adolescents, with separate inhalers (Jorenby, J Allergy Clin Immunol 2015)
- Three RCTs showed similar or fewer exacerbations compared with maintenance ICS
  - TREXIA, BEST
  - BASALT in adults, separate inhalers, vs physician-adjusted treatment (Calhoun, JAMA 2012)

Values and preferences
- High importance given to preventing severe exacerbations
- Lower importance given to small differences in symptom control and the inconvenience of needing to carry two inhalers

Another option: leukotriene receptor antagonist (less effective for exacerbations)
Step 1 – ‘preferred’ controller option

- Step 1 is for patients with symptoms less than twice a month, and with no exacerbation risk factors

  As-needed low dose ICS-formoterol (off-label)

  Evidence
  - Indirect evidence from SYGMA 1 of large reduction in severe exacerbations vs SABA-only treatment in patients eligible for Step 2 therapy (O’Byrne, NEJM 2018)

  Values and preferences
  - High importance given to reducing exacerbations
  - High importance given to avoiding conflicting messages about goals of asthma treatment between Step 1 and Step 2
  - High importance given to poor adherence with regular ICS in patients with infrequent symptoms, which would expose them to risks of SABA-only treatment

Step 1 - other controller option

  Low dose ICS taken whenever SABA is taken (off-label)

  Evidence
  - Indirect evidence from studies in patients eligible for Step 2 treatment (BEST, TREXA, BASALT)

  Values and preferences
  - High importance given to preventing severe exacerbations
  - Lower importance given to small differences in symptom control and the inconvenience of needing to carry two inhalers
  - Combination ICS-SABA inhalers are available in some countries, but approved only for maintenance use

Daily ICS is no longer listed as a Step 1 option

- This was included in GINA 2014-18, but with high probability of poor adherence
- Now replaced by more feasible as-needed controller options for Step 1

Other changes in GINA 2019 - Steps 3-5 for adults and adolescents

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GINA 2018 – main treatment figure

Step 1 treatment is for patients with symptoms twice/month and no history for exacerbations.

Previously, no controller was recommended for treatment was ‘preferred’. Now, personalized treatment for individual needs.

Step 1 – Low dose ICS

- Reliever: As needed
- Controller: Enter as Step 2

Adjust treatment up and down for response.

Assess, Personalization, goals.

GINA 2018 Pocket Guide for Adults & adolescents 12+

See severe asthma

Mark needs for details about Step 5.
Changes in GINA 2019 – children 6-11 years

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Other controller options
- Leukotriene receptor antagonist (LTRA), or
  low dose ICS taken whenever SABA taken*
- Low dose ICS + LTRA
- High dose ICS - LABA, or add - on tiotropium,
  or add - on LTRA
- Add - on anti-IL5,
  or add - on low dose OCS,
  but consider side effects

Low dose ICS taken whenever SABA taken*;
  or daily low dose ICS

RELIEVER* Off-label; separate ICS and SABA inhalers;
  only one study in children

PREFERRED CONTROLLER to prevent exacerbations and control symptoms

Step 1
- Low dose ICS whenever SABA taken (indirect evidence), or daily low dose ICS

Step 2
- Preferred controller is daily low dose ICS
  - Other controller options include as-needed low dose ICS taken whenever SABA is
taken, but only one study in children (Martinez, Lancet 2015)
  - Studies of as-needed ICS-formoterol are needed; maintenance and reliever therapy
  with low-dose budesonide-formoterol in children 4-11 years reduced exacerbations
  by 70-79% compared with ICS and ICS-LABA (Bisgaard, Chest 2006)

Step 3
- Low dose ICS-LABA and medium dose ICS are ‘preferred’ controller treatments
  - No safety signal with ICS-LABA in children 4-11 years (Stampel, NEJM 2017)

Step 4
- Medium dose ICS-LABA, but refer for expert advice
Other changes in GINA 2019 – severe asthma

- Pocket guide about difficult-to-treat and severe asthma
  - A practical guide for primary and specialist care
  - Includes a decision tree about assessment and management of adults and adolescents with uncontrolled asthma or exacerbations despite Step 4-5 treatment
  - Includes strategies for clinical settings in which biologic therapy is not available or affordable
  - First published in November 2018
- V2.0 Pocket Guide published April 2018
  - Also included in full GINA 2019 report
  - Includes anti-IL4 receptor alpha (dupilumab)
  - Extension of biologic treatment trial to 6-12 months if response to initial therapy is unclear
Updated strategies for ‘yellow zone’ of action plans, with new evidence
- 4x increase in ICS dose decreased severe exacerbations in pragmatic study in adults (McKeever, NEJMed 2018)
- 5x increase in ICS dose did not decrease severe exacerbations in children with good symptom control and high adherence (Jackson, NEJMed 2018)

Pre-school asthma
- Additional suggestions for investigating history of wheezing episodes
- Early referral recommended if child fails to respond to controller treatment
- For exacerbations, OCS not generally recommended except in ED setting
- Follow-up after ED or hospital: within 1-2 working days and 3-4 weeks later
- Pocket guide on management of asthma in children 5 years and younger will be updated in 2019