Asthma Guidelines: EPR-3 & 4, GINA and Yardsticks

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Disclosures

• **Research:** Clinical trials - GSK, Genentech, AstraZeneca, SANOFI, TEVA

• **Consultation/Advisory Board:** – TEVA, GSK, AstraZeneca, SANOFI, Genentech, Novartis
Objectives

After this session participants will be able to:

• Have an increased understanding of asthma phenotypes
• Describe the asthma paradox and change in approaches to management of mild asthma
• Demonstrate understanding of GINA guidelines in 2019 and the use of asthma yardsticks
• Have an overview of the use of biologics in the treatment of severe asthma
Asthma is a chronic disease characterized by recurrent episodes of:

- wheezing
- shortness of breath and
- cough secondary to reversible airflow obstruction

Bronchial hyperresponsiveness & airway Inflammation are hallmarks of asthma

Asthma is a complex disorder that has many distinct pathophysiological mechanisms contributing to clinical signs and symptoms.
The asthma subject has denuded epithelium, mucous gland hypertrophy, thickened reticular basement membrane and inflammatory cell infiltration in the mesenchyme.

Obtained from Busse et al. NEJM. 344;350-362.
What are asthma phenotypes and are they important?
Phenotype to Endotype

- Phenotype – the observable properties of an organism that are produced by the interaction of the genotype and the environment.

- Endotype - An "endotype" is proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism. Criteria for defining asthma endotypes on the basis of their phenotypes and putative pathophysiology are suggested.
We have now moved to defining phenotypes of this heterogeneous disease

**Clinical:**
- Fixed obstruction
- Obese
- Adult onset
- Exacerbation prone
- Treatment resistant

**Pathologic:**
- Eosinophilic
- Non-eosinophilic
- Pauci-granulocytic

Phenotype suggests a clustering of characteristics, but may not describe underlying pathobiology that create these characteristics

**Triggers**
- Occupational
- Aspirin
- Exercise
- Menses
Phenotypes to Endotypes

The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1 | Endotype 2 | Endotype 3 | Endotype 4 | Endotype 5

FIG 1. Asthma is made up of different endotypes, each characterized by its pathophysiology.

Endotype: underlying biologic or pathobiologic mechanism

Lotvall et al. JACI 2011;127:355-60
Emphasis Shifting from Empiric to Targeted (Precision) Therapy

Relationship Between Blood Eosinophil Counts and Asthma Exacerbations

Claims database analysis examining eosinophil counts and exacerbations requiring systemic CS or ER/hospital care (N=61,841)

Sputum Eosinophils are Associated with Asthma Severity

Louis et al, Am J Respir Crit Care Med, 2000
Sputum Eosinophils Are Associated with Asthma Exacerbations

Green et al, Lancet, 2002
Sputum Eosinophils Impact Response to Inhaled Asthma Therapies

A Differential Response to Three Trial Agents

- Mometasone vs. Placebo
  - Mometasone or placebo better: 50%
  - Neither better: 30%

- Tiotropium vs. Placebo
  - Tiotropium or placebo better: 60%
  - Neither better: 20%

B Primary Analysis

- Mometasone vs. Placebo: P = 0.14
- Tiotropium vs. Placebo: P = 0.029
Baseline predictors of response to benralizumab treatment

Five clinical predictors of response with benralizumab were identified:
- OCS use
- Nasal polyps
- Pre-BD FVC <65%
- ≥3 exacerbations
- ≥18 years of age at asthma diagnosis

Annual exacerbation rate reduction vs placebo %

- OCS use: Yes 62%, No 38%
- Nasal polyps: Yes 54%, No 38%
- Pre-BD FVC: <65% 54%, ≥65% 37%
- Exacerbations: ≥3 55%, 2 27%
- Age at diagnosis: ≥18 50%, <18 21%
- Either OCS use, nasal polyps, pre-BD FVC <65% of predicted or age at diagnosis ≥18 years

#Nominal P-value <0.001; †Nominal P-value >0.01–≤0.05

Patients with eosinophil counts at baseline ≥300 cells/µL. Patient population had high-dosage ICS/LABA. All P-values were nominal.

BD, bronchodilator; FAS, full analysis set; FVC, forced vital capacity; LABA, long-acting β2-agonist; OCS, oral corticosteroid

Review of Current NAEPP Guidelines and Ongoing Updates
## Classifying Severity in Patients ≥12 Years Not Currently Taking Long-Term Controllers

### Components of Severity

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Classification of Asthma Severity (Youths ≥12 of Age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>&lt;2x/month</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>• Normal FEV₁ between exacerbations</td>
</tr>
<tr>
<td></td>
<td>• FEV₁ &gt;80% predicted</td>
</tr>
</tbody>
</table>

### Impairment

<table>
<thead>
<tr>
<th>Normal FEV₁/FVC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-19 yr 85%</td>
</tr>
<tr>
<td>20-39 yr 80%</td>
</tr>
<tr>
<td>40-59 yr 75%</td>
</tr>
<tr>
<td>60-80 yr 70%</td>
</tr>
</tbody>
</table>

### Risk

<table>
<thead>
<tr>
<th>Exacerbations (consider frequency and severity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2/year</td>
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</tbody>
</table>

**Frequency and severity may fluctuate over time.**

Relative annual risk of exacerbations may be related to FEV₁.

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Emphasizing Control Rather Than Severity

Asthma Control

- Good
- Poor

Mild

Severe

Asthma Severity

- good control
- Control reflects the adequacy of treatment
- We have little influence!
- In which we play a significant role!
- Severity is a property of the disease
- poor control

We have little influence! In which we play a significant role!

Severity is a property of the disease

Control reflects the adequacy of treatment

good control
NAEPP Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age

| Step 1 | PREFERRED | • Intermittent Asthma  
|        |           | • SABA PRN  

| Step 2 | PREFERRED | • Low-dose ICS  
|        | ALTERNATIVE | • Cromolyn, Nedocromil, LTRA, or Theophylline  

| Step 3 | PREFERRED | • Medium-dose ICS OR Low-dose ICS + LABA  
|        | ALTERNATIVE | • Low-dose ICS + either LTRA, Theophylline, or Xileuton  

| Step 4 | PREFERRED | • Medium-dose ICS + LABA  
|        | ALTERNATIVE | • Medium-dose ICS + either LTRA, Theophylline, or Xileuton  

| Step 5 | PREFERRED | • High-dose ICS + LABA  
| AND | • Consider Omalizumab for patients who have allergies  

| Step 6 | PREFERRED | • High-dose ICS + LABA + oral corticosteroid  
| AND | • Consider Omalizumab for patients who have allergies  

- **Persistent Asthma: Daily Medication**
  - Consult with asthma specialist if step 4 care or higher is required.
  - Consider consultation at step 3.

- 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 systemic oral corticosteroids may be needed.
  - Caution: Increasing of beta-agonist or use >2x/week for symptom control indicates inadequate control and the need to step up treatment.

- Patient Education and Environmental Control at Each Step

- 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)
Updates NAEPP Guidelines Ongoing

• Intermittent use of ICS and long acting muscarinic antagonists in asthma
  – Includes intermittent ICS dosing/use of ICS/LABA as reliever therapy

• Effectiveness and safety of bronchial thermoplasty in asthma management

• Fraction of exhaled nitric oxide clinical utility in asthma management

Mensah et al. JACI 2018; 142:744-748
Updates NAEPP Guidelines Ongoing

• Effectiveness of indoor allergen reduction in asthma management

• The role of immunotherapy and asthma management
  – Covers both subcutaneous and sublingual immunotherapy

Mensah et al. JACI 2018; 142:744-748
GINA (Global Initiative for Asthma) Strategy 2019 Updates
Background to changes in 2019 - the risks of ‘mild’ 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

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Background to changes in 2019 - the risks of SABA-only treatment

• Regular or frequent use of SABA is associated with adverse effects
  – β-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)
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’
**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

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

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

**STEP 2**
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

**STEP 3**
Low dose ICS-LABA
Medium dose ICS, or low dose ICS+LTRA #

**STEP 4**
Medium dose ICS-LABA
High dose ICS, add-on tiotropium, or add-on LTRA #

**STEP 5**
High dose ICS-LABA
Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IL5/5R, anti-IL4R
Add low dose OCS, but consider side-effects

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

**Treatment of modifiable risk factors & comorbidities**
Non-pharmacological strategies
Education & skills training
Asthma medications

**Symptoms**
**Exacerbations**
**Side-effects**
**Lung function**
**Patient satisfaction**

**Confirmation of diagnosis if necessary**
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**Adults & adolescents 12+ years**

**Personalized asthma management:**
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**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**
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *

Low dose ICS taken whenever SABA is taken †

As-needed low dose ICS-formoterol *

Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

**STEP 2**
Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

STEP 3
Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

**STEP 4**
Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

Add low dose OCS, but consider side-effects

**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)

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Patient goals

Treatment of modifiable risk factors & comorbidities

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Education & skills training

Asthma medications

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

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

Add low dose OCS, but consider side-effects

Confirmation of diagnosis if necessary

Symptom control & modifiable risk factors (including lung function)

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Exacerbations
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Patient satisfaction

**STEP 4**
Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

Add low dose OCS, but consider side-effects

Confirmation of diagnosis if necessary

Symptom control & modifiable risk factors (including lung function)

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Asthma medications

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

**STEP 3**
Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

STEP 2
As-needed low dose ICS-formoterol *

Low dose ICS taken whenever SABA is taken †

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

As-needed low dose ICS-formoterol *

As-needed short-acting β₂-agonist (SABA)

As-needed short-acting β₂-agonist (SABA)

As-needed low dose ICS-formoterol ‡

Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

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

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## Personalized asthma management:
Assess, Adjust, Review response

### Symptoms
- Exacerbations
- Side-effects
- Lung function
- Patient satisfaction

### Treatment of modifiable risk factors & comorbidities
- Non-pharmacological strategies
- Education & skills training
- Asthma medications

### Controller’ treatment means the treatment taken to prevent exacerbations

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

#### PREFERRED CONTROLLER
- to prevent exacerbations and control symptoms
- Low dose ICS-LABA
- Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken

#### Other controller options
- As-needed low dose ICS-formoterol *
- As-needed short-acting β₂-agonist (SABA)

#### PREFERRED RELIEVER
- Other reliever option
- As-needed low dose ICS-formoterol *

### As-needed low dose ICS-formoterol *
- Off-label; data only with budesonide-formoterol (bud-form)

### As-needed short-acting β₂-agonist (SABA)

### As-needed low dose ICS-formoterol ‡
- Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

### As-needed low dose ICS-formoterol †
- Off-label; separate or combination ICS and SABA inhalers

### As-needed low dose ICS-formoterol *
- Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

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

## STEP 2
- Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *
- Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken †

## STEP 3
- Low dose ICS-LABA
- Medium dose ICS-LABA
- High dose ICS, add-on tiotropium, or add-on LTRA #

## STEP 4
- Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R
- Add low dose OCS, but consider side-effects

## STEP 5
- High dose ICS-LABA
- Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

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

### Symptoms
- Exacerbations
- Side-effects
- Lung function
- Patient satisfaction

### Box 3-5A
Adults & adolescents 12+ years

### Symptom control & modifiable risk factors (including lung function)
- Comorbidities
- Inhaler technique & adherence
- Patient goals

### Confirmation of diagnosis if necessary
- Symptom control & modifiable risk factors (including lung function)
- Comorbidities
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- Patient goals
**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

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

**OTHER CONTROLLER OPTIONS**

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**STEP 1**
As-needed low dose ICS-formoterol

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

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

† Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

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

**STEP 3**
Medium dose ICS-LABA

**STEP 4**
High dose ICS-LABA

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

Add low dose OCS, but consider side-effects

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

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Education & skills training
Asthma medications
**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

**PREFERRED CONTROLLER**
to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**
Other reliever option

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**STEP 1**
As-needed low dose ICS-formoterol *

**STEP 2**
Low dose ICS taken whenever SABA is taken†

**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

Add low dose OCS, but consider side-effects

**Confirmation of diagnosis if necessary**
Symptom control & modifiable risk factors (including lung function)
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Step 2 - other controller options

Low dose ICS taken whenever SABA taken (off-label, separate or combination inhalers)

• Evidence
  – Two RCTs showed reduced exacerbations compared with SABA-only treatment
    • BEST, in adults, with combination ICS-SABA *(Papi, NEJM 2007)*
    • TREXA, in children/adolescents, with separate inhalers *(Martinez, Lancet 2011)*
  – Three RCTs showed similar or fewer exacerbations compared with maintenance ICS
    • TREXA, 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
  – Combination ICS-SABA inhalers are available in some countries, but approved only for maintenance use

• Another option: leukotriene receptor antagonist (less effective for exacerbations)

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Box 3-5A

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
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Lung function
Patient satisfaction

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

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

STEP 1
Daily low dose inhaled corticosteroid (ICS), or as-needed low dose ICS-formoterol *

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

STEP 2
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

STEP 3
Low dose ICS-LABA

Medium dose ICS-LABA

STEP 4
Refer for phenotypic assessment ± add-on therapy, e.g. tiotropium, anti-IgE, anti-IL5/5R, anti-IL4R

STEP 5
High dose ICS-LABA

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
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Patient goals

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Asthma medications

Step 4 treatment is medium dose ICS-LABA; high dose now in Step 5

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Symptom control & modifiable risk factors (including lung function)
Comorbidities
Inhaler technique & adherence
Patient goals

Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (including lung function)
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**Step 1**

As-needed low dose ICS-formoterol *

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**Step 3**

Low dose ICS-LABA

Medium dose ICS, or low dose ICS+LTRA #

**Step 4**

Medium dose ICS-LABA

High dose ICS, add-on tiotropium, or add-on LTRA #

**Step 5**

High dose ICS-LABA

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

Add low dose OCS, but consider side-effects

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**Asthma medication options:**

Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**

to prevent exacerbations and control symptoms

**PREFERRED RELIEVER**

Other reliever option

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**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 goals

**Treatment of modifiable risk factors & comorbidities**

Non-pharmacological strategies

Education & skills training

Asthma medications

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**See severe asthma Pocket Guide for details about Step 5**

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ATS/ERS Severe Asthma Definition

- Asthma that requires GINA steps 4-5 medications (high dose ICS and LABA and LTRA/theophylline for one year OR systemic CS ≥ 50% of the prior year to prevent loss of control.

- Uncontrolled asthma is defined as:
  - Poor symptom control, ACT <20, ACQ > 1.5
  - Frequent severe exacerbations ≥ 2 x/ year
  - At least one hospitalization, ICU stay of mechanical ventilation in past year
  - FEV1 < 80% with reduced FEV1/FVC

Chung et al. ERJ 2014; 43:343-373
Biologics for Severe Asthma Therapy

Confirm diagnosis of severe asthma. If not adherent, provide patient education, frequent follow-up visits, evaluate factors associated with non-adherence. Evaluate adherence to GINA steps 4-5 medications.

Phenotype Evaluation:
- Spirometry
- Assess asthma control
- Assess asthma symptoms
- Assess for allergies
- Assess asthma history e.g., age of asthma onset, family history of asthma
- Assess exacerbations including steroid bursts and healthcare utilization
- Assess comorbidities e.g., GERD, severe sinus disease, obesity, OSA, recurrent LRTI

Biomarker Evaluation:
- Allergy sensitization evaluation:
  - Skin prick Testing or Radioallergosorbent testing
- Total IgE level
- Complete blood count with differential
- Fraction of exhaled nitric oxide

Phenotype and biomarker evaluation.

Airway Epithelial and Goblet Cells

Severe allergic phenotype
- AMG 317
- Lebrikizumab
- Tralokinumab
- Dupilumab
- Omalizumab
- IgE
- Mast Cell
- Hay fever, seasonal exacerbations, allergen sensitization, high IgE

Severe eosinophilic phenotype
- IL-4Rα
- Dupilumab
- IL-4
- IL-23
- Lebrikizumab
- Tralokinumab
- Dupilumab
- Mepolizumab
- Reslizumab
- IL-5
- Th2 Cell
- B Cell
- Evidence of eosinophilic inflammation with or without evidence of atopy.

Severe asthma with physiologic impairment

Severe neutrophilic phenotype
- APC
- IL-8
- CXCR 1/2
- Neutrophil
- Brodalumab
- IL-17
- IL-6, IL-8
- Macrolides
- Non-allergic asthma may have low degree of eosinophilic inflammation

Omalizumab Decreases Seasonal Asthma Exacerbations

FeNO: 53% (95% [CI], 37–70; P=0.001) versus 16% (95% CI, 32 to 46; P 0.45)

Eosinophils: 32% (95% CI, 1148; 0.005) versus 9% (95% CI, 24 to 34; P 0.54)

Periostin: 30% (95% CI, 2 to 51; P=0.07) versus 3% (95% CI, 43 to 32; P=0.94).


Hanania et al. AJRCCM. 2012;187:804-811
Mepolizumab Significantly Decreased Blood Eosinophils, Exacerbations and Improved Lung Function

Asthma Exacerbations were reduced by 47% with IV mepolizumab and 53% with SC mepolizumab

Mepolizumab significantly reduces eosinophil counts by week 4 of therapy

At week 32, the mean increase from baseline FEV1 was 100ml greater in the IV mepo grp (p=0.02) and 98ml greater in the SC group (p=0.03)

Ortega HG et al. NEJM 2014. 371:1198-1207
Benralizumab in Severe Eosinophilic Asthma

Mepolizumab Decreased OCS Dose and Reduced Exacerbations Despite Significant Reduction in OCS Use

At 24 weeks, mean % reduction from baseline OCS dose was 50% in mepo group and no reduction in the placebo group

Relative reduction of 32% in exacerbations Compared with placebo (p=0.04)
Steroid Sparing Effects of Benralizumab in Severe Eosinophilic Asthma

Nair et al. NEJM 2017
Reslizumab in Severe Eosinophilic Asthma

- In two studies, the probability of not having an exacerbation by week 52 with placebo was 44% (95% CI 38–51) and 52% (95% CI 45–58), and with Reslizumab it was 61% (95% CI 55–67) and 73% (95% CI 67–79), respectively.

- Reslizumab reduced the risk for asthma exacerbation compared with placebo in both studies (P < 0.0001)

Dupilumab Significantly Decreases OCS and Exacerbations in Moderate to Severe asthma

A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Placebo</th>
<th>Dupilumab</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>317</td>
<td>631</td>
<td>0.52 (0.41–0.66)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤300 cells/mm³</td>
<td></td>
<td>148</td>
<td>264</td>
<td>0.34 (0.24–0.48)</td>
</tr>
<tr>
<td>≥300 to ≤300 cells/mm³</td>
<td></td>
<td>84</td>
<td>173</td>
<td>0.64 (0.41–1.02)</td>
</tr>
<tr>
<td>&gt;300 cells/mm³</td>
<td></td>
<td>85</td>
<td>193</td>
<td>0.93 (0.58–1.47)</td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td></td>
<td>71</td>
<td>119</td>
<td>0.31 (0.18–0.52)</td>
</tr>
<tr>
<td>≥25 to ≤50 ppb</td>
<td></td>
<td>91</td>
<td>180</td>
<td>0.39 (0.24–0.62)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td></td>
<td>149</td>
<td>325</td>
<td>0.75 (0.54–1.05)</td>
</tr>
</tbody>
</table>

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Placebo</th>
<th>Dupilumab</th>
<th>Relative Risk vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>321</td>
<td>631</td>
<td>0.54 (0.43–0.68)</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤300 cells/mm³</td>
<td></td>
<td>142</td>
<td>277</td>
<td>0.33 (0.23–0.45)</td>
</tr>
<tr>
<td>≥300 to ≤300 cells/mm³</td>
<td></td>
<td>95</td>
<td>175</td>
<td>0.56 (0.35–0.89)</td>
</tr>
<tr>
<td>&gt;300 cells/mm³</td>
<td></td>
<td>83</td>
<td>181</td>
<td>1.15 (0.75–1.77)</td>
</tr>
<tr>
<td>FENO</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 ppb</td>
<td></td>
<td>75</td>
<td>124</td>
<td>0.31 (0.19–0.49)</td>
</tr>
<tr>
<td>≥25 to ≤50 ppb</td>
<td></td>
<td>97</td>
<td>186</td>
<td>0.44 (0.28–0.69)</td>
</tr>
<tr>
<td>&lt;25 ppb</td>
<td></td>
<td>144</td>
<td>317</td>
<td>0.79 (0.57–1.10)</td>
</tr>
</tbody>
</table>

Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FENO.

FENO denotes fraction of exhaled nitric oxide, and ppb parts per billion.

GINA Severe Asthma Algorithm

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes cont’d

Continue to optimize management as in section 3 (including inhaler technique, adherence, comorbidities)

6b Consider add-on biologic Type 2 targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations or poor symptom control on high dose ICS-LABA, who:
  - have eosinophilic or allergic biomarkers, or
  - need maintenance OCS
- Consider local payer eligibility criteria and predictors of response when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

**Anti-IgE**
- Is the patient eligible for anti-IgE for severe allergic asthma?
  - Sensitization on skin prick testing or specific IgE
  - Total serum IgE and weight within dosage range
  - Exacerbations in last year
  - Blood eosinophils ≥250 μl

What factors may predict good asthma response to anti-IgE?
- Blood eosinophils ≥250 μl
- FeNO ≥20 ppb
- Allergen-driven symptoms
- Childhood-onset asthma

**Anti-IL5 / Anti-IL5R**
- Is the patient eligible for anti-IL5 / anti-IL5R for severe eosinophilic asthma?
  - Exacerbations in last year
  - Blood eosinophils ≥300 μl

What factors may predict good asthma response to anti-IL5/5R?
- Higher blood eosinophils
- More exacerbations in previous year
- Adult-onset of asthma
- Nasal polyposis

**Anti-IL4R**
- Is the patient eligible for anti-IL4R... for severe eosinophilic asthma?
  - Exacerbations in last year
  - Blood eosinophils ≥150 μl or FeNO ≥25 ppb
  - or because of need for maintenance OCS?

What factors may predict good asthma response to anti-IL4R?
- Higher blood eosinophils
- Higher FeNO
- Anti-IL4R may also be used to treat
  - Moderate/severe atopic dermatitis
  - Nasal polyposis

Good asthma response?

- Yes: Good response to T2-targeted therapy
- No: Continue with add-on biologic

Choose one if eligible, trial for at least 4 months and assess response

Extend trial to 6-12 months

Choose one if eligible, trial for at least 4 months and assess response

Little/no response to T2-targeted therapy

Consider switching to a different Type 2-targeted therapy, if eligible

STOP add-on

Eligible for none?

Return to section 6a
**ATS/ERS Updated Guidelines 2019**

- Blood eosinophil cut off of ≥150/ul can be used to guide anti IL5 therapy

- Eosinophil count of ≥260/ul or a FeNO >19.5ppb can be used to guide use of anti IgE therapy. Patients with both biomarkers have the best response

- Consider a trial of chronic macrolide therapy to decrease exacerbations in adults with persistently symptomatic or uncontrolled asthma on step 5 therapy

Holguin et al. ERJ 2019; In press
ATS/ERS Updated Guidelines 2019

• Suggest the use of anti IL5 and IL5r antibodies for the treatment of severe eosinophilic asthma (SEA)

• Suggest tiotropium for adults and adolescents >18 years of age with uncontrolled asthma on GINA step 4 or 5 therapy, irrespective of phenotype

• Suggest antiIL4/13 therapy in adults with SEA and OCS dependent asthma regardless of eosinophil count
Asthma Yardstick
# Asthma Yardstick

## Classification of asthma control

<table>
<thead>
<tr>
<th>Control component</th>
<th>Well controlled</th>
<th>Not well controlled</th>
<th>Very poorly controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days per week</td>
<td>&gt;2 days per week</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2 times per month</td>
<td>1–3 times per week</td>
<td>≥4 times per week</td>
</tr>
<tr>
<td>Interference with normal activities</td>
<td>None</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Using SABA for symptoms (not prevention of EIB)</td>
<td>≤2 days per week</td>
<td>&gt;2 days per week</td>
<td>Several times per day</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; or PEF</td>
<td>&gt;80% predicted/personal best</td>
<td>60%–80% predicted/personal best</td>
<td>&lt;80% predicted/personal best</td>
</tr>
</tbody>
</table>

## Validated questionnaires

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>≥20</td>
<td>16–19</td>
<td>≤15</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75</td>
<td>≥1.5</td>
<td>NA</td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
<td>1–2</td>
<td>3–4</td>
</tr>
</tbody>
</table>

## Risk

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations requiring OCS</td>
<td>≤1 per year</td>
<td>≥2 per year</td>
<td></td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Long-term follow-up required</td>
<td>Long-term follow-up required</td>
<td>Long-term follow-up required</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>May vary from none to troublesome/or worrisome. Intensity does not correlate with level of control but should be considered in overall assessment of risk.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Asthma Yardstick

Evaluate why the patient is experiencing not well-controlled or poorly controlled asthma (increased symptoms, lower lung function [eg, PEF, FEV1], acute events)
Are the symptoms due to asthma alone and not to other factors (eg, poor adherence, improper inhaler technique, infection, environmental exposures)?

How long has the patient experienced not well-controlled or poorly controlled asthma?

- Short period (< 1 week)
  - Symptoms satisfactorily treated with a short-acting bronchodilator (until worsening has passed or until increased controller medication takes effect)
  - No step-up needed

- Prolonged period (≥ 8 weeks) despite patient following his/her asthma action plan
  - Symptoms (with or without change in lung function) confirmed due to asthma and not poor adherence or other factors
  - Consider a sustained step-up
Asthma Yardstick

Stepping Up From GINA Step 2 to Step 3 - Patient Profile:
Symptomatic* ≥ 2 months or 2 or more exacerbations requiring OCS in past year, despite preferred treatment for mild, persistent asthma (i.e., low-dose ICS monotherapy) and optimal adherence**

- Switch to low-dose ICS/LABA
- OR increase ICS dose
- OR add LTRA or SRT

3-month therapeutic trial with reassessment at 2-6 weeks

Stepping Up From GINA Step 3 to Step 4 - Patient Profile:
Symptomatic* ≥ 2 months or 2 or more exacerbations requiring OCS in past year, despite using low dose ICS/LABA (OR medium-dose ICS, ICS and SRT, OR ICS and LTRA) and optimal adherence**

- Refer to asthma specialist
- Continue to optimize medication:
  - Increase to medium, then high dose ICS/LABA, AND/OR
  - Add inhaled corticosteroids, AND/OR
  - Add small-particle ICS (or use small-particle ICS/LABA)

3-month therapeutic trial with reassessment at 2-6 weeks

Stepping Up From GINA Step 4 to Step 5 - Patient Profile:
Difficult-to-treat asthma: Symptomatic* ≥ 2 months or 2 or more exacerbations requiring OCS in past year, despite using high doses of anti-inflammatory and bronchodilator medications and optimal adherence**

- Asthma specialist care required

Targeting Treatment - Patient Profile: IgE (allergic)
Difficult-to-treat characteristics and moderate-to-severe allergic asthma (with total serum IgE = 30-700 IU/mL) and demonstrated IgE-mediated hypersensitivity to a perennial allergen***

- Add omalizumab

3-month therapeutic trial with interval reassessment

Targeting Treatment - Patient Profile: Eosinophilic
Difficult-to-treat asthma and eosinophilic phenotype (current or history of blood eosinophils > 300 cells/μL and 2 or more exacerbations requiring OCS in past year OR current or history of ≥150 cells/μL and 3 or more exacerbations requiring OCS in past year)

- Add anti-IL-5

3-month therapeutic trial with interval reassessment

Targeting Treatment - Patient Profile: Neutrophilic
Difficult-to-treat asthma and sputum neutrophils in patients who do not respond to high doses of corticosteroids and do not have other type 2 markers

- Consider adding a macrolide antibiotic

3-month therapeutic trial with interval reassessment

Targeting Treatment - Patient Profile: Airway Smooth Muscle Hypertrophy
Patient with difficult-to-treat asthma profile who doesn’t qualify for other targeted therapies and/or has tried and failed targeted therapies for which s/he might be eligible and demonstration of variable airflow obstruction by bronchodilator reversibility

- Consider bronchial thermoplasty in addition to regular treatment

3-month therapeutic trial with interval reassessment
Figure 2. Recommendations for stepping down asthma therapy. Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic agent; LM, leukotriene modifier; OCS, oral corticosteroid; QD, once-a-day; SABA, short-acting beta₂-agonist.
Questions?