Asthma Phenotypes: Implications for Targeted Treatment Choices

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Definition of Severe Asthma > age 6

(ATS/ERS Guidelines; ERJ 2014;43:343)

Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 asthma (high dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for > 50% of the previous year to prevent it from becoming “uncontrolled” or which remains “uncontrolled” despite this therapy.
Stepwise Approach for Managing Asthma in Patients ≥ 12 Years of Age

**STEP 1**
- PREFERRED
- Low-dose ICS
- SABA PRN

**STEP 2**
- PREFERRED
- Low-dose ICS
- Cromolyn, Nedocromil, LTRA, or Theophylline

**STEP 3**
- PREFERRED
- Medium-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

**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.

The GINA Report Has A More Updated Treatment Approach for Adults, Adolescents & Children (ages 6-11)

**PREFERRED CONTROLLER CHOICE**

- **STEP 1**
  - Consider low-dose ICS

- **STEP 2**
  - Leukotriene receptor antagonists (LTRA)
  - Low-dose theophylline*

- **STEP 3**
  - Low-dose ICS/LABA**
  - Med/high-dose ICS/LABA

- **STEP 4**
  - Med/high-dose ICS
  - Low-dose ICS+LTRA (or + theoph*)
  - Add tiotropium**
  - Add low-dose OCS

- **STEP 5**
  - Refer for add-on treatment e.g. tiotropium,** anti-IgE, anti-IL5*

**RELIEVER**

- As-needed short-acting beta₂-agonist (SABA)

- As-needed SABA or low dose ICS/formoterol#

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

<table>
<thead>
<tr>
<th>Question</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is this asthma?</td>
<td>Confirm Asthma Diagnosis</td>
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<tr>
<td></td>
<td>History/Physical</td>
</tr>
<tr>
<td></td>
<td>Spirometry with reversibility and chest x-ray</td>
</tr>
<tr>
<td></td>
<td>Address medication adherence, technique</td>
</tr>
<tr>
<td>What is contributing to the asthma?</td>
<td>Further Evaluate Suspected Severe Asthma</td>
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<tr>
<td></td>
<td>Assess and manage comorbidities</td>
</tr>
<tr>
<td></td>
<td>Atopy, Allergic Bronchopulmonary aspergillosis,</td>
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<tr>
<td></td>
<td>chronic sinusitis, chronic obstructive pulmonary disease, gastro-esophageal reflux disease, vocal</td>
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<tr>
<td></td>
<td>cord dysfunction, obstructive sleep apnea, obesity, depression</td>
</tr>
<tr>
<td>Is this severe asthma?</td>
<td>Confirm Severe Asthma</td>
</tr>
<tr>
<td></td>
<td>Plethysmography, DLCO</td>
</tr>
<tr>
<td></td>
<td>Methacholine challenge, FeNO if available</td>
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<tr>
<td></td>
<td>Biomarkers: Blood eosinophils, IgE</td>
</tr>
<tr>
<td></td>
<td>Imaging: High resolution CT scan of lungs</td>
</tr>
<tr>
<td></td>
<td>Treatment options beyond guidelines</td>
</tr>
<tr>
<td>What would a referral center add?</td>
<td>Additional workup for phenotyping, comorbidities</td>
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<tr>
<td></td>
<td>Additional Therapeutics</td>
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<td>Small particle devices</td>
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<td>Novel investigational interventions</td>
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</table>
Key Concepts

- Asthma is a syndrome with many nonspecific features
- Thorough history, physiologic and radiographic assessment to confirm diagnosis
- Once confirmed, the severity and control, in addition to the asthma phenotype is determined.
What is Asthma?

- Early onset
- Late onset

Symptoms

Exacerbations

FEV1

TH2 inflammation
- Eosinophilic
- Non-eosinophilic

Phenotype A
Phenotype B
Phenotype C
Phenotype D

Understanding Disease Mechanisms May Guide Therapy to a More Personalized Approach

One Size Fits All  Stratified Medicine  Personalized Medicine

- Evidence-based
  - One treatment for all

- Evidence-based
  - Different treatments for groups of patients

- Evidence-based
  - Individualized treatment for each patient

Asthma Phenotypes

- **Phenotype**: observable properties of an organism that are produced by the interactions of the genotype and the environment.

- Asthma phenotypes are based on clinical characteristics, triggers or general inflammatory processes have been proposed and do not always suggest an underlying mechanism.

- **Endotype**: a specific biological pathway is identified that explains the observable properties of a phenotype.
Th2/T2 asthma

- T2/Th2-associated asthma linked to:
  - atopy and allergy
    - type I hypersensitivity reactions
    - eosinophilic inflammation and response to corticosteroids

- Early-onset (preadolescence) mostly atopic and allergic asthma phenotype
  - Strong family history of atopic disease
  - Overlap with other co-morbid atopic conditions: allergic rhinitis and atopic dermatitis
  - Early-onset allergic asthma can present with mild to severe disease; unclear whether mild allergic asthma progresses to severe disease or whether severe allergic asthma arises in childhood and remains severe
  - Can be exacerbated by obesity
Th2/T2 Asthma

- Later-onset (often age 20 or later) eosinophilic phenotype
  - Approx 50% asthma associated with high EOS (>2% in sputum; no consistent serum value)
  - In severe asthma, high numbers of eosinophils can persist despite treatment with inhaled and oral corticosteroids and appear to be consistent over at least 5 yrs
  - Tends not to be allergic, related to family history
  - Usually severe from the outset
  - Can be related to sinus disease, polyp formation and aspirin sensitivity…AERD
  - Exacerbated/associated by obesity
Non-T2/Th2 asthma/non-eosinophilic

- Non-T2/Th2 asthma is likely to represent a large proportion of all asthma (up to 50% OCS-naïve pts) but little is understood about pheno/endotypes
- Responds poorly to corticosteroid therapy
- Linkage to obesity (esp in age>40)
- “Neutrophilic” asthma: may be driven by OCS use; associated with lower lung function, more air trapping, thicker airway walls
- Associations also present with infections, and environmental exposures (ozone, pollutants)
Overview of Asthma Phenotypes

Adapted from Wenzel S. Nature Medicine 18, 716–725 (2012)
Multiple Endotypes Drive Asthma Phenotypes

**TABLE I. Proposed relationship between asthma phenotypes and endotypes: asthma phenotypes can be present in more than 1 endotype, and endotypes can contain more than 1 phenotype**

| Phenotype: | Eosinophilic asthma |
| Endotypes: | allergic asthma (adult),* aspirin-sensitive asthma, severe late-onset hypereosinophilic asthma,* ABPM* |

| Phenotype: | Exacerbation-prone asthma |
| Endotypes: | allergic asthma (adult),* aspirin-sensitive asthma,* late-onset hypereosinophilic asthma, API-positive preschool wheezer,* ABPM,* viral-exacerbated asthma, premenstrual asthma |

| Phenotype: | Obesity-related asthma |
| Endotypes: | airflow obstruction caused by obesity, severe steroid-dependent asthma, severe late-onset hypereosinophilic asthma* |

| Phenotype: | Exercise-induced asthma |
| Endotypes: | cross-country skiers’ asthma, other forms of elite-athlete asthma, allergic asthma, API-positive preschool wheezer* |

| Phenotype: | Adult-onset asthma |
| Endotypes: | aspirin-sensitive asthma,* infection-induced asthma, severe late-onset hypereosinophilic asthma* |

| Phenotype: | Fixed airflow limitation |
| Endotypes: | noneosinophilic (neutrophilic) asthma |

| Phenotype: | Poorly steroid-responsive asthma |
| Endotypes: | noneosinophilic (neutrophilic) asthma, steroid-insensitive eosinophilic asthma, airflow obstruction caused by obesity |

Biomarkers to identify the Th2 phenotype

- Sputum eosinophils
- Exhaled nitric oxide
- Circulating eosinophils
- IgE
- Allergen skin testing
- Eosinophil Peroxidase – in development
- Urinary bromotyrosine – in development
Mechanisms of Eosinophilic/T2 Asthma

EPX is increased in eosinophilic asthma and correlates with sputum eosinophils

Rank et al. Allergy 2016;7:567
Is asthma uncontrolled, despite stepping up to a high-dose ICS + LABA?

- Poor symptom control (ACQ > 1.5, ACT < 20, or per GINA/NAEPP guidelines)
- ≥2 bursts of systemic corticosteroids for asthma exacerbations in the past year
- ≥1 hospitalization for asthma in the past year
- FEV₁ < 80% predicted when not taking short- or long-acting bronchodilators
- Asthma is uncontrolled when any 1 of the 4 criteria above is present

Close follow-up. Reduce treatment intensity after at least 3-6 months of stable, good control, per GINA/NAEPP guidelines.

Consider adding a non-biologic therapy
- Tiotropium
- Leukotriene modifier
- Theophylline
- Macrolide antibiotic
- Oral glucocorticoid (short course)

is asthma still uncontrolled, despite treatment with high-dose ICS + LABA and a non-biologic add-on therapy?

Refer patient to an asthma specialist

Determine inflammatory phenotype/Endotype
- Start with non-invasive testing (allergy testing, IgE level, blood eosinophil count and FENO level)
- If poor response to therapy continues, consider induced sputum differential for eosinophil and neutrophil counts and/ or bronchoscopy with endobronchial biopsy and BAL
Treatments approved or under development

Adapted from Muraro et al. JACI 2016 137, 1347-1358
How Does Omalizumab Compare With New Biologics In Similar Patients?

Effect of omalizumab based on Th2 biomarkers

- FeNO
  - <19.5 ppb
  - ≥19.5 ppb
- Eosinophils
  - <260/µL
  - ≥260/µL
- Periostin
  - <50 ng/mL
  - ≥50 ng/mL

Reduction in protocol-defined Asthma exacerbation rate (Mean %, 95% CI)

- FeNO
  - n = 193
  - P = 0.45*
  - n = 201
  - P = 0.001*
- Eosinophils
  - n = 383
  - P = 0.54*
  - n = 414
  - P = 0.005*
- Periostin
  - n = 279
  - P = 0.94*
  - n = 255
  - P = 0.07*

*Exacerbation reduction P-values; omalizumab versus placebo in each biomarker subgroup.

Anti-IL-5/IL-5R Biologics

- Efficacy data most compelling if peripheral eos > 300/µl with improved lung function and decreased exacerbations
- Can consider if peripheral eos > 150/µl
- Consider if eos elevated and atopy not as clinically significant but can be a challenging decision
- Consider if patient requiring oral steroids yet demonstrates peripheral eosinophils, especially if > 300/µl
The DREAM Study
Dose-Ranging Efficacy of Mepolizumab in Reducing Exacerbation

Mepolizumab: *NEJM* 2014

**Asthma exacerbations**

<table>
<thead>
<tr>
<th>Cumulative no.</th>
<th>Placebo</th>
<th>Mepolizumab 75 IV</th>
<th>Mepolizumab 100 SC</th>
</tr>
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<tbody>
<tr>
<td>Week 0-32</td>
<td></td>
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**Change from baseline in glucocorticoid**

<table>
<thead>
<tr>
<th>Median change (%)</th>
<th>Placebo (n = 66)</th>
<th>Mepolizumab (N = 69)</th>
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<td>Week 0-24</td>
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**FEV$_1$**

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<tr>
<th>FEV$_1$ (% of predicted value)</th>
<th>Placebo</th>
<th>Mepolizumab 75 IV</th>
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IV = intravenous; SC = subcutaneous.
Reslizumab—Effects on Exacerbations and Lung Function

Placebo; n = 244
Reslizumab 3.0 mg/kg; n = 245
HR = 0.575 (95% CI 0.440–0.750)
P<0.0001

CAE = clinical asthma exacerbation; HR = hazard ratio; LS = least square (mean).

Benralizumab Reduced Frequency of Asthma Exacerbations (Primary Endpoint)

Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations

Eosinophil ≥300 cells per µL

- Placebo (n=267)
- Benralizumab 30 mg Q4W (n=275)
- Benralizumab 30 mg Q8W (n=267)

Percentage reduction relative to placebo

- 45%
- 51%

Annual asthma exacerbation rate ratio (95% CI)

- 1.12-1.58
- 0.60-0.89
- 0.53-0.80

P < 0.0001

Eosinophil <300 cells per µL

- Placebo (n=140)
- Benralizumab 30 mg Q4W (n=124)
- Benralizumab 30 mg Q8W (n=131)

Percentage reduction relative to placebo

- 30%
- 17%

Annual asthma exacerbation rate ratio (95% CI)

- 0.96-1.52
- 0.65-1.11
- 0.78-1.28

P = 0.047

P = 0.0269

Benralizumab Reduced Time to Asthma Exacerbation

- Benralizu-mab administered every 4 weeks was associated with a longer time to the first exacerbation than placebo (HR, 0.39; 95% CI, 0.22 to 0.66; \(P<0.001\))
- Benralizumab administered every 8 weeks was also associated with a longer time to the first exacerbation than placebo (HR, 0.32; 95% CI, 0.17 to 0.57; \(P<0.001\))

Benralizumab Reduced Oral Glucocorticoid Dose in Severe Asthma (Primary Endpoint)

- 75% median reduction from baseline in the final oral glucocorticoid dose in patients who received Either of the benralizumab regimens, vs 25% in the patients who received placebo ($P<0.001$ for both comparisons)
Dupilumab Phase III data

Dupilumab is Corticosteroid Sparing

2019: Non-T2 options (not only T2)
Peripheral eos < 150/µl
FeNO < 19 ppb
Sputum eos < 2%

- Tiotropium
- Macrolides
- Bronchial thermoplasty
Treatments under development – Non T2

- Neutrophilic inflammation
- Paucigranulocytic inflammation
- Airway hyperreactivity and remodeling

- imatinib

- ILC1/3?
- Epithelium
- Neutrophil
- Th1
- Th17

- Macrolides
  - proteases
  - ROS
  - IL-1
  - IL-6

- Bacterial products
  - IFN-γ
  - TNF-α

- IL-8
- IL-23

- Bronchial Thermoplasty

- IL-17
  - IL-18
  - IL-22
  - IL-23
  - CXCR2

Adapted from Muraro et al. JACI 2016 137, 1347-1358
Tezepelumab Reduces Severe Asthma Exacerbations Independent of Blood Eosinophil Count

FeNo = Fractionated nitric oxide; Ppb = Parts per billion.
Blood Eosinophils

Fevipiprant in Eosinophilic Asthma

- Significantly reduced eosinophilic inflammation in the sputum and bronchial submucosa in patients with persistent moderate to severe asthma and sputum eosinophilia
- Significantly improved AQLQ(S) scores, postbronchodilator FEV₁, and functional residual capacity in all patients, and ACQ-7 scores in the predefined subgroup of patients who had uncontrolled asthma at baseline
- Favorable safety profile, with no deaths or serious AEs reported; no withdrawals related to the study drug

Our Approach to Asthma is Changing

- Our understanding of the biology of asthma heterogeneity has improved dramatically.
- The use of clinical characteristics, biomarkers and response to treatment will further hone our ability to deliver personalized/precision therapy.
- We need readily available point-of-care biomarkers to make real time decisions regarding therapies for our patients.