Management of Severe Asthma Including Biologics and Bronchial Thermoplasty

Karen L. Gregory, DNP, APRN, CNS, RRT, AE-C, FAARC
Disclosures

• ALK – speaker
• Monaghan Medical Corporation – speaker
• Novartis – speaker
Management of Severe Asthma Including Biologics and Bronchial Thermoplasty

• Describe characteristics and components of airway pathophysiology in severe asthma including remodeling.
• Discuss challenges in the diagnosis, management, and phenotyping of severe asthma.
• Identify key features of evaluation, management, and targeted therapies of severe asthma.
Severe Asthma
International ERS/ATS Guidelines

When a diagnosis of asthma is confirmed and comorbidities have been addressed, severe asthma is defined as:

“asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.”

Severe Asthma

- Major cause of morbidity and health care costs, and affects 10% of all patients with asthma that is, approximately 2.5 million Americans\(^1,2\)
- Challenging to assess and control due to heterogeneity of disease, complexity of diagnosis, and impact of comorbidities\(^2\)
- Poor response to the standard treatment contributing to increased health care utilization, costs, and morbidity\(^3,4\)

2. Carr TF, Kraft M. Management of severe asthma before referral to the severe asthma specialist. J Allergy Clin Immunol Pract 2017;5:877-86
Clinical Features Associated with Increased Risk of Severe Exacerbations

- Poor symptom control
- One or more severe exacerbations in the previous year
- High short-acting beta-agonist use
- Exposure to tobacco smoke
- High allergen exposure
- Poor lung function
- Comorbidities including obesity and rhinosinusitis
- Major psychosocial problems

Predictors of Exacerbation in Patients with Severe Asthma

Type 2 biomarkers

- Peripheral blood eosinophils
- Fractional exhaled nitric oxide (FENO)
- Serum periostin
- Serum IgE

Identifying Life Threatening or Deterioration Asthma

- Infants < 1 year old
- Prior history of life-threatening exacerbation
- Less than 10% PEF in emergency department
- PEF or FEV1 < 25% predicted value
- PaCO2 > 40 mmHg
- Wide daily fluctuations in PEF
- Patients who cannot recognize airflow obstruction

National Asthma Education and Prevention Program
Airway Remodeling

Airway remodeling is associated with local matrix deposition, vascularization, epithelial hyperplasia and changes in the submucosa, such as smooth muscle cell hyperplasia and fibroblast proliferation.

Two types of airway remodeling:

1. **Physiological airway remodeling**: encompasses structural changes that occur regularly during normal lung development and growth leading to a normal mature airway wall or as an acute and transient response to injury and/or inflammation, which ultimately results in restoration of a normal airway structures.

2. **Pathological airway remodeling**: comprises those structural alterations that occur as a result of either disturbed lung development or as a response to chronic injury and/or inflammation leading to persistently altered airway wall structures and function.

---


Epithelial Damage
Severe Asthma

1. Confirm Asthma Diagnosis
2. Identify comorbidities
3. Recognize and correct poor adherence
4. Asthma Education – errors in medication administration
5. Patient-specific phenotypes and endotypes
Confirm Severe Asthma

Body plethysmography  DLCO
Methacholine challenges
FeNO
Biomarkers – IgE, eosinophils
Computed tomography of the chest
Chest x-ray

• Additional workup for phenotyping
• Additional workup for comorbidities
• Treatment options beyond guidelines
Identify Comorbidities

Atopy
Allergic Rhinitis
Allergic Bronchopulmonary Aspergillosis
Bronchiectasis
Chronic Obstructive Pulmonary Disease

Chronic Rhinosinusitis
Gastroesophageal Reflux Disease
Vocal Cord Dysfunction
Obesity
Obstructive Sleep Apnea
Psychological/Depression
Adherence

- Despite the availability of effective therapies over half of patients with asthma appear to be poorly controlled largely due to poor adherence\(^1\)
- 80% of patients with difficult-to-treat asthma have poor adherence with regular inhaled therapy
- In patients with corticosteroid-dependent asthma only half take oral corticosteroids regularly


Carr TF, Kraft M. Management of severe asthma before referral to the severe asthma specialist. J Allergy Clin Immunol Pract 2017;5:877-86
Systematic Assessment of Adherence and Persistent Triggers

- Does the patient understand the concept of inhaled therapy for asthma control?
- Is the patient receiving basic inhaled therapy according to guidelines and adapted to the severity of their asthma?
- Does the patient administer inhaler(s) correctly?
- Does the patient take inhaled therapy regularly?
- Does the patient avoid smoking and second and third hand tobacco smoke exposure?
- Does the patient know their allergen spectrum and effectively avoid these allergens?
- Does the patient avoid detrimental medications?

Assessment and Management of Severe Asthma

- Ineffective drug delivery
- Medication Nonadherence
- Financial Barriers
- Effective provider-patient communication
- Asthma Education
Stepwise management - pharmacotherapy

**Diagnosis**
- Symptom control & risk factors (including lung function)
- Inhaler technique & adherence
- Patient preference

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

**ASSESS**
- Asthma medications
- Non-pharmacological strategies
- Treat modifiable risk factors

**REVIEW RESPONSE**

**ADJUST TREATMENT**

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

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

**STEP 3**
- Med/high ICS/LABA
  - Med/high dose ICS
  - Low dose ICS + LTRA (or + theoph*).

**STEP 4**
- Med/high dose ICS + LTRA
  - Add tiotropium**
  - Add low dose OCS

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

**PREFERRED CONTROLLER CHOICE**

**RELIEVER**
- As-needed short-acting beta-agonist (SABA)
- As-needed SABA or low dose ICS/formoterol*

*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

GINA 2018, Box 3-5 (2/8) (upper part)
# GINA assessment of symptom control

## A. Symptom control

<table>
<thead>
<tr>
<th>In the past 4 weeks, has the patient had:</th>
<th>Well-controlled</th>
<th>Partly controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime asthma symptoms more than twice a week?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any night waking due to asthma?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reliever needed for symptoms* more than twice a week?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any activity limitation due to asthma?</td>
<td>Yes ☐ No ☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **None of these**
- **1-2 of these**
- **3-4 of these**

## B. Risk factors for poor asthma outcomes

- Assess risk factors at diagnosis and periodically
- Measure FEV₁ at start of treatment, after 3 to 6 months of treatment to record the patient’s personal best, then periodically for ongoing risk assessment

**ASSESS PATIENT’S RISKS FOR:**
- Exacerbations
- Fixed airflow limitation
- Medication side-effects
Phenotyping Asthma
Phenotyping of Asthma

Severe asthma tends to be characterized by ongoing symptoms and airway inflammation despite treatment with high doses of inhaled and systemic corticosteroids, there is increasing recognition of marked phenotypic heterogeneity within affected patients.

Carr TF, Kraft M. Management of severe asthma before referral to the severe asthma specialist. J Allergy Clin Immunol Pract 2017;5:877-86
Phenotyping and Endotyping Asthma

- Asthma was first phenotyped by Rackemann, who classified the disease as allergic or extrinsic and nonallergic or intrinsic\(^1\)
- Defined as observable characteristics that may or may not be associated with underlying disease mechanisms
- Phenotyping integrates biological and clinical features, ranging from molecular, cellular, morphological and functional to patient-oriented characteristics with the goal to improve therapy\(^2\)
- A phenotype can be considered the external manifestation of an individual’s underlying genetics on interaction with environment
- Asthma can be organized into phenotypes and endotypes on the basis of observable and/or clinical characteristics\(^3\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Association</th>
<th>Specifically target treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe allergic asthma</td>
<td>Blood and sputum eosinophils, High serum IgE, High FeNO</td>
<td>Anti-IgE (adults and children), Anti-IL-4/IL-13, Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Eosinophilic asthma</td>
<td>Blood and sputum eosinophils, Recurrent exacerbations, High FeNO</td>
<td>Anti-IL-5, Anti-IL-4/IL-13, Anti-IL-4 receptor</td>
</tr>
<tr>
<td>Neutrophilic asthma</td>
<td>Corticosteroid insensitivity, Bacterial infections</td>
<td>Anti-IL-8, CXCR2 antagonists, Anti-LTB4 (adults and children), Macrolides (adults and children)</td>
</tr>
<tr>
<td>Chronic airflow obstruction</td>
<td>Airway wall remodeling as increased airway wall thickness</td>
<td>Anti-IL-13, Bronchial thermoplasty</td>
</tr>
<tr>
<td>Recurrent exacerbations</td>
<td>Sputum eosinophils in sputum, Reduced response to ICS and/or OCS</td>
<td>Anti-IL-5, Anti-IgE (adults and children)</td>
</tr>
<tr>
<td>Corticosteroid insensitivity</td>
<td>Increased neutrophils in sputum</td>
<td>p38 MAPK inhibitors, Theophylline, Macrolides</td>
</tr>
</tbody>
</table>

Biomarkers

- Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention.

- Several inflammatory phenotypes have been identified by the use of biomarkers.

- All of the current biomarkers available in clinical practice are focused on type 2 “allergic” inflammation (blood eosinophils, exhaled nitric oxide [FeNO], sputum eosinophils). Sputum eosinophils have been the “gold standard” type 2 inflammatory biomarker.


Evaluation and Asthma Management

1. **Symptom control**: to achieve good control of symptoms and maintain normal activity levels

2. **Risk reduction**: to minimize future risk of exacerbations, fixed airflow limitation and medication side-effects

Achieving these goals requires a partnership between patient and their health care providers:

- Ask the patient about their own goals regarding their asthma
- Good communication strategies are essential
- Consider the health care system, medication availability, cultural and personal preferences and health literacy

Asthma Control Test
Pediatric
Asthma Action Plan

- All patients should have a written asthma action plan
  - The aim is to show the patient how to recognize and respond to worsening asthma
  - It should be individualized for the patient's medications, level of asthma control and health literacy
  - Based on symptoms and/or PEF (children: only symptoms)
- The action plan should include:
  - asthma medications
  - when/how to increase reliever and controller or start OCS
  - how to access medical care if symptoms fail to respond
- When combined with self-monitoring and regular medical review, action plans are highly effective in reducing asthma mortality and morbidity

Pharmacologic Management
Pharmacologic Management

- Inhaled corticosteroids (ICS)
- Short-acting bronchodilators (SABA)
- Long-acting bronchodilators (LABA)
- Combination ICS/LABA
- Systemic corticosteroids
- Leukotriene modifiers
- Anti-immunoglobulin E (IgE) and anti-interleukin-5 (IL-5) antibodies
- Ipratropium bromide
- Tiotropium bromide
- Theophylline
Targeted Therapies for Severe Asthma
Biologic Therapeutics

Biologic treatments aim to treat T2 high asthma and the therapeutic options for T2 low asthma is limited

Therapies that target key cells and mediators that drive inflammatory responses in asthma

Moderate or severe persistent asthma with particular phenotypes

Heterogeneity of asthma results in varying responses to therapies

Must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis.
Anti-IgE

Binds free IgE, reduces circulating free IgE and downregulates its high-affinity receptor FceRI on basophils and mast cells.

Disrupts the allergic signaling cascade by preventing interaction of IgE with immune cells essential to inflammation.

IgE is a key component of atopic asthma pathophysiology.
Omalizumab (Xolair)

- Indication: moderate to severe persistent asthma ≥ 6 years old who have a positive skin test or in vitro reactivity to aeroallergen and whose symptoms are inadequately controlled with ICS

- The dose and frequency is based on body weight and levels of serum IgE, 150-375 mg every 2 to 4 weeks

  - IgE 30 – 700 IU/ml > 12 years
  - IgE 30- 1300 IU/ml 6-12 years
  - Weight: 44- 330 lbs

Not indicated for acute bronchospasm or status asthmaticus

FDA approved June, 2003
Pediatric approval July, 2016
Genentech and Novartis

Omalizumab [package insert]
Anti-IL 5

- IL-5 is a cytokine produced by a number of cell types.
- Essential for the maturation of eosinophils in the bone marrow and their release into the blood.
- IL-5 acts only on eosinophils and basophils causing maturation, growth, activation and survival.
- Only eosinophils and basophiles possess IL-5 receptors.
Anti-IL-5

IL-5 is essential for eosinophil maturation, activation, and survival.

Anti-IL-5 therapies target eosinophilic inflammation.
Mepolizumab (Nucula)

- Monoclonal antibodies against IL-5 that are FDA approved for the treatment of severe eosinophilic asthma
- Eosinophils ≥ 150 cells/uL
- Indication: Add-on maintenance therapy for severe persistent asthma ≥12 years old with an eosinophil phenotype
- 100 mg subcutaneous injection every 4 weeks
- Not indicated for acute bronchospasm or status asthmaticus

Glaxo Smith Kline

FDA approval 2015.

Mepolizumab [package insert]
Benralizumab Fasenra

- Targets Anti-IL 5 receptor
- Produces a dose-dependent reduction in blood eosinophils.
- Effects can last up to 8 to 12 weeks after single dosing.
- Added benefit of inducing apoptosis in cells expressing the IL-5 receptor
- Appears to have a glucocorticoid sparing effect in patients required oral glucocorticoids for severe asthma
- Benralizumab showed significant, clinically relevant benefits, as compared with placebo, on oral glucocorticoid use and exacerbation rates.
- No sustained effect on the FEV1
- Approved November, 2017

AstraZeneca

Reslizumab (Cinqair)

- Interleukin-5 antagonist monoclonal antibody (IgG4 kappa) indicated for add-on maintenance treatment of patients with severe asthma ≥ 18 years old and with an eosinophilic phenotype

- 400 cells/ mcL (within 3 to 4 weeks of dosing) and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months

- Reslizumab is an intravenous formulation that is administered once monthly

- Recommended dosage regimen is 3 mg/kg once every 4 weeks by intravenous infusion over 20-50 minutes

- Injection: 100 mg/10 mL (10 mg/mL) solution in single-use vials

TEVA Pharmaceutical

FDA approval 2016

Reslizumab [package insert]
Clinical Trials
Anti-IL 13
Anti-IL-4

- IL-13 induces eosinophil recruitment to lung tissue
- Anti-IL 13: tralokinumab and lebrikizumab
Anti-TSLP therapies: Tezepelumbab

- TSLP –
  - an epithelial-derived cytokine that acts upstream to promote allergic inflammation
  - Released in response to various stimuli
  - Acts on innate immune cells to increase the number of Th2, IL-5, IL-13 production and blood and airway eosinophils
  - Inhibits early and late allergic response to allergen challenge
  - Results in a decreased in blood and sputum eosinophils and FeNO during nonallergen challenge phase of study
CRT\textsubscript{H2} antagonism: Fevipiprant

- CRT\textsubscript{H2} antagonist
- Inhibits prostaglandin D2 receptor 2 (driver of inflammation in eosinophilic asthma)
- Reduced airway inflammation compared to placebo in uncontrolled moderate-to-severe eosinophilic asthma
- Phase III clinical trials
- Twice-day oral pill
Tyrosine kinase inhibition: Imatinib

- Decreased airway hyper-responsiveness measured by concentration of methacholine required to decrease FEV1 by 20% compared to placebo
- Reduced markers of mast cell activation
- Eosinophils counts were inversely correlated with reduced airway hyper-responsiveness – may be more effective in patients with non-allergic phenotype
Bronchial Thermoplasty
 Bronchial Thermoplasty

- Indicated for patients with severe asthma despite optimal medical therapy
- Prednisone burst 3 to 5 days prior to procedure
- PFT performed the day of procedure
- BT is not performed if there is evidence of infection or an exacerbation
- Application of radiofrequency energy to the airways distal to the mainstem bronchi to airways as small as 3 mm in diameter
- Three bronchoscopic sessions at 2 to 3 week intervals
- In clinical trials bronchial thermoplasty had an acceptable safety profile while improving asthma quality-of-life scores, symptoms, and health care utilization
Bronchial Thermoplasty
What if the medical treatment regimen is not working?
Difficult-to-Control Asthma

- Misdiagnosis
  another respiratory system pathology → bronchiectasis, endo-bronchial tumors, vocal cord dysfunction
- Comorbidity
- Confounding factors → Nonadherence, environmental, psychosocial
- Alternative pharmacological therapies indicated

Failure to Achieve Control

Asthma heterogeneity

Failure to deliver drug to the target site

Adherence to medical treatment regimen

Implementation of asthma education

Often times, patients treat asthma as an acute, episodic illness rather than a chronic disease.
Referral to a Specialist

- Life threatening exacerbation or frequent hospitalizations/ER visits
- Signs and symptoms are atypical
- Problems with a differential diagnosis or comorbidities
- Additional testing or education is indicated
- Patient is not meeting goals of asthma therapy after 3 months of treatment
- Patient requires continuous oral corticosteroid therapy or high dose inhaled corticosteroids
- Adult patient requires step 4 care or higher
- Pediatric patient requires step 3 care or higher
Summary

- Asthma is a heterogeneous inflammatory disorders characterized different phenotypes with distinct genetic components, environmental causes, and immunopathologic components.
- Patients with severe asthma tend to be characterized by ongoing symptoms and airway inflammation despite treatment with high doses of inhaled and systemic corticosteroids.
- Phenotyping allows to predict who best will respond to therapies and optimize quality of life by reducing the risk of exacerbations.
- Biological therapeutics are for use in severe asthma with pre-specified phenotypes or biomarkers.
- An appropriate treatment regimen, management plan, and asthma education are vital to achieve and maintain asthma control.
Thank you!

kgregory@oklahomaallergy.com
kg559@georgetown.edu