Severe Childhood Asthma

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Objectives

- Discuss the challenges in diagnosing severe asthma in children
- Learn a systematic approach to diagnose and manage this disease
- Briefly review future steps in this field

Outline

- Definition
- Epidemiology
- Diagnosis
- Treatment
- Next Steps

Definition

- Probably the largest challenge
- It is not the same as:
  - Difficult-to-treat asthma
  - Poorly controlled asthma
  - Severe refractory asthma
Definition

Epidemiology

- ~5-10% of all pediatric asthma
- ~30-50% of all pediatric asthma costs
- More common in:
  - Teenagers
  - Females after puberty
  - African Americans and Puerto Ricans
  - Low socioeconomic status
  - Children with comorbidities
Epidemiology

- Onset of symptoms are usually in the first 24 months of life
- Symptoms persist into adulthood in the vast majority of cases

Diagnosis

- Not asthma at all
- Asthma plus
- Difficult-to-treat asthma
- Severe refractory asthma

Not asthma at all

- Cystic fibrosis
- Non-cystic fibrosis bronchiectasis
- Primary ciliary dyskinesia
- Airway malacia or compression
- Congenital lung lesions
- Recurrent aspiration
- Vocal cord dysfunction
- Retained foreign body
- Habit cough
- Cardiovascular diseases

- Bronchiolitis obliterans
- Hypersensitivity pneumonitis
- Interstitial lung disease
- Immunodeficiency
- Sarcoidosis
- Pulmonary edema
- Parasitic lung infections
- Eosinophilic granulomatosis with polyangiitis

Not asthma at all

- Pre- and post-bronchodilator spirometry
- Body plethysmography
- Fractional exhaled nitric oxide (FeNO)
- Complete blood count with differential
- Total immunoglobulin E (IgE)
- Skin and/or blood allergy testing
- Chest radiograph
- High-resolution chest computed tomography
- Sweat test
- Echocardiogram
- Video fluoroscopic swallow study
- Flexible bronchoscopy with bronchoalveolar lavage
- Pediatric ENT and GI evaluation
Figure. Flow-volume curve

A: Variable extrathoracic central airway obstruction (e.g., vocal cord dysfunction or upper airway malacia)
B: Peripheral airway obstruction (e.g., asthma or cystic fibrosis)
C: Fixed intrathoracic or extrathoracic central airway obstruction (e.g., subglottic stenosis or upper airway tumors)
D: Variable intrathoracic central airway obstruction (e.g., lower airway malacia or compression)

Chipps BE et al, Ann Allergy Asthma Immunol 2010

Figure. Volume-time curve

Jarjour NN et al, Am J Respir Crit Care Med 2012

Figure. Body Plethysmography

Indig JN et al, Am J Respir Crit Care Med 2012
Seventh Pediatric Asthma Education Conference

**Asthma plus**
- Allergic diseases
- Chronic sinusitis
- Nasal polyps
- Airway malacia or compression
- Vitamin D deficiency
- Exposure to tobacco smoke
- Environmental pollutants
- Obesity
- Obstructive sleep apnea
- Gastroesophageal reflux disease
- Recurrent aspiration
- Hyperventilation syndrome
- Fungal sensitization and colonization
- Endocrine disorders
- Psychosocial issues
- Poor perception of symptoms

**Difficult-to-treat asthma**
- 10% of patients never fill their prescription for inhaled steroid
- 50% are not adherent
- Patients find asthma medications:
  - Complex
  - Useless
  - Risky
  - Expensive

**Shake the asthma inhaler and attach it to a spacer device**
- Breathe out completely
- Apply mask to face and ensure effective seal or seal your lips tightly around the mouthpiece
- Press the inhaler
- Breathe in slowly and completely through your mouth
- Hold your breath for ≥10 seconds to allow the medication to deposit in your lungs
- Remove the spacer and breathe out slowly
- Wait for about 3 minutes and then repeat above steps for every puff or inhaler order
- Gargle and rinse your mouth with water after each use
Severe refractory asthma

- Asthma that remains uncontrolled after:
  - The resolution of any reversible factor
  - The optimization of basic management
- ~50% of uncontrolled asthma
- Merits a detailed assessment and individualized treatment plan
- Requires evaluation by a specialized center

Treatment

- Inflammation

- Bronchoconstriction

Treatment

- Assess pattern of inflammation:
  - Non-invasive methods: Complete blood count with differential, total IgE, skin and/or blood allergy testing, FeNO, induced sputum
  - Invasive methods: Bronchial wash, bronchoalveolar lavage, bronchial brushing, endobronchial biopsy

Treatment

- Assess steroid response:

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom score</td>
<td>Asthma control test, rescue dose of albuterol, or by at least 5 years</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV1 - ratio to normal (J in 95% of cases) or by 15%</td>
</tr>
<tr>
<td>Inflammatory (if paired)</td>
<td>Sputum eosinophil count normal (≤5%)</td>
</tr>
<tr>
<td>Inflammatory (if paired)</td>
<td>Fractional exhaled nitric oxide normal (&lt;10 parts per billion)</td>
</tr>
</tbody>
</table>

Bush A et al, Lancet 2010
Inflammation

- Inhaled steroids (ICS):
  - Fine-particle ICS
  - High-dose ICS
- Systemic steroids:
  - Oral
  - Parenteral
- Monoclonal antibodies:
  - Omalizumab
  - Mepolizumab
  - Benralizumab
- Leukotriene antagonists:
  - Zileuton
- Theophylline
- Macrolides?
- Immunosuppressants?

Bronchoconstriction

- β2-adrenergic agonists:
  - As-needed long-acting beta agonists (LABAs)
  - Ultra-LABAs (not approved for children)
- Theophylline
- Long-acting anticholinergics:
  - Tiotropium
- Bronchial thermoplasty (not approved in children)

Treatment

- Fine-particle ICS:
  - Include beclomethasone dipropionate (Qvar), ciclesonide (Alvesco), and flunisolide (Aerobid)
  - Make sense but there is no strong evidence
  - May be more expensive and may not be covered by insurance

<table>
<thead>
<tr>
<th>Particle Size</th>
<th>Median Absorption (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4 micron</td>
<td>1.9</td>
</tr>
<tr>
<td>1.1 micron</td>
<td>0.7</td>
</tr>
<tr>
<td>2.1 micron</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Small particles are more likely to reach both the large and small airways.

Leach C et al, J Allergy Clin Immunol 2009
Treatment

• High-dose ICS:
  - May be beneficial and even safe
  - High-dose for inhaled steroids has been arbitrarily defined
  - Inhaled steroids are safer than systemic steroids
  - Steroid resistance is a spectrum

• Oral steroids:
  - There is no clear evidence for the:
    - Starting dose
    - Frequency of administration
    - Duration of the trial
    - Tapering regimen

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Treatment

• Parenteral steroids:

<table>
<thead>
<tr>
<th>Asthma severity marker</th>
<th>Parenteral</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of exacerbations (n)</td>
<td>3.3 (0.78)</td>
<td>0.1 (0.30)</td>
<td>0.1 (0.29)**</td>
</tr>
<tr>
<td>Oral prednisolone dose (mg)</td>
<td>31 (29)</td>
<td>46 (2)</td>
<td>8.8 (0.52)**</td>
</tr>
<tr>
<td>Days requiring oral steroids (n)</td>
<td>17 (8.5)</td>
<td>1.2 (1.7)**</td>
<td>1.9 (0.55)**</td>
</tr>
<tr>
<td>Hospital admissions (n)</td>
<td>0 (0.78)</td>
<td>0.2 (0.39)**</td>
<td>0.1 (0.15)**</td>
</tr>
<tr>
<td>Duration of hospital admission (days)</td>
<td>3.2 (2.3)</td>
<td>0.3 (0.7)**</td>
<td>0.4 (0.7)**</td>
</tr>
</tbody>
</table>

*Data are summarized as mean (SD) per month, and compared with pre-treatment period by paired t-test.

**P < 0.05.

***P < 0.01.

Jeyachandran R et al, Pediatr Allergy Immunol 2010

Treatment

• As-needed LABAs:

[Graphs and images related to treatment options]
Treatment

• Omalizumab (Xolair):
  - Humanized monoclonal antibody against IgE
  - Approved for children 6 years and older
  - Administered SC every 2-4 weeks
  - Dose depends on total IgE level and child’s weight

From: www.xolair.com

• Mepolizumab (Nucala):
  - Humanized monoclonal antibody against interleukin 5 (IL-5)
  - Approved for children 12 years and older
  - Administered SC every 4 weeks
  - Indicated for eosinophilic atopic asthma

From: www.gsksource.com

• Benralizumab (Fasenra):
  - Humanized monoclonal antibody against the IL-5 receptor
  - Approved for children 12 years and older
  - Administered SC every 4-8 weeks
  - Indicated for eosinophilic atopic asthma

From: www.fasenrahcp.com
Treatment

• Zileuton (Zyflo):

- Scow DT et al, Am Fam Physician 2007

<table>
<thead>
<tr>
<th>Table 1: Leukotriene Inhibitors for the Treatment of Allergy and Asthma</th>
<th>Age and recommended dosage</th>
<th>Approximate dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Age and recommended dosage</td>
<td>Approximate dosage</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Zileuton</td>
<td>1 year and older</td>
<td>5 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>2 years and older</td>
<td>10 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>3 years and older</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>4 years and older</td>
<td>25 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>125 mg twice daily</td>
</tr>
</tbody>
</table>

- Serum levels need to be monitored
- Risk for acute and chronic toxicity

Next Steps

• Standardization of the definition
• Identification of potentially modifiable risk factors
• Better understanding of the pathophysiology
• Better characterization of phenotypes
• Management of non-atopic childhood asthma
• Randomized controlled trials in young children

Treatment

• Theophylline:

- Barnes PJ et al, Am J Respir Crit Care Med 2013

- At high doses, acts like a bronchodilator
- At low doses, acts like an anti-inflammatory
- Serum levels need to be monitored
- Risk for acute and chronic toxicity

- Theophylline: At high doses, acts like a bronchodilator. At low doses, acts like an anti-inflammatory. Serum levels need to be monitored. Risk for acute and chronic toxicity.

- Tiotropium: Long-acting anticholinergic agent. Administered once a day. Approved for children 6 years and older. May take several weeks to take effect.

Next Steps

Table 1: Biological drugs in asthma treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipomim</td>
<td>Inhibits IL-33, decreases airway hyperresponsiveness and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Remicade</td>
<td>Inhibits TNF-alpha, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Inhibits TNF-alpha, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Humira</td>
<td>Inhibits TNF-alpha, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Inhibits JAK3, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Inhibits TGF-beta, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vocentis</td>
<td>Inhibits PD-1, decreases airway inflammation and eosinophilia</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*Development phases: Phase I - Phase III.
When should you refer a patient?

- If you think it may be not be asthma
- If there are multiple comorbidities
- If it is not controlled on standard therapy
- If adherence has been adequately addressed

Questions?

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