Pediatric Asthma Update

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Outline

• Asthma
  • Definition
  • Risk factors
  • Natural history
  • Asthma phenotypes
  • Evaluation
  • Diagnosis
  • Mimickers/Comorbidities of Asthma
  • Treatment
• Conclusion
Definition

- "Asthma"—from greek verb "aazein"
  - to pant, exhale with open mouth, or sharp breath

- Chronic inflammation of the airway
  - Leading to symptoms such as—
    - Cough
    - SOB
    - Chest tightness
    - Wheezing
Clinical Definition

Recurring symptoms suggestive of asthma

+ Evidence of reversible airflow on spirometry testing
  (or bronchoprovocation testing)
Risk Factors for Asthma

1. Gene-environment interaction
   - Genetically-susceptible individual exposed to environmental trigger
   - Asthma more prevalent in certain ethnic groups/families
     - Puerto Ricans > African Americans > Caucasians

2. Sex
   - Before puberty—Male > Female
   - After puberty—Female > Male
Risk Factors for Asthma

3. Atopy
   - Aeroallergen exposure
     - Dust mites, cockroach, mold (Alternaria)
     - 40% of allergic rhinitis patients have asthma\(^1\)
     - 80% of asthmatic patients have allergic rhinitis\(^1\)

4. Respiratory infections
   - RSV (<2 yrs) and rhinovirus (>2 yrs)

5. “Hygiene hypothesis”

6. Tobacco smoke

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http://www.worldallergy.org/public/allergic_diseases_center/caras/
Risk Factors for Asthma

7. Air pollution
8. Occupational exposure
   • Plant dusts, enzymes, chemicals, etc
9. Diet (controversial)
   • Lack of breastfeeding, insufficient whole grains, fish, etc
10. Obesity
Natural History of Asthma

- Infants and Children\(^1-3\)
- **3 TYPES:**

1. Transient early wheezers
   - 60% who wheeze in first 3 yrs of life, “outgrow” wheezing by age 6 yrs
   - NOT TRUE ASTHMA
   - Virus-induced swelling of small-diameter airways leads to wheezing sound

\(^1\)NEJM 1995, \(^2\)NEJM 2000, \(^3\)JACI 1996
Natural History of Asthma

- Infants and Children\textsuperscript{1-3}

- 3 TYPES:

  2. Persistent wheezers

  - Wheezing starts < 3 yrs of age and persists beyond age 6 yrs
    - Tend to be atopic (eczema, allergic rhinitis, or food allergy)
    - Maternal asthma
    - Maternal tobacco use
  - TRUE ASTHMA

\textsuperscript{1NEJM 1995, 2NEJM 2000, 3JACI 1996}
Natural History of Asthma

• Infants and Children\(^1\)-\(^3\)

• **3 TYPES:**

3. Later-onset wheezers
   • Wheezing occurs around 3-4 yrs of age and persists into adulthood
   • TRUE ASTHMA

\(^1\)NEJM 1995, \(^2\)NEJM 2000, \(^3\)JACI 1996
Natural History of Asthma

• Asthma effects on lung function\textsuperscript{1,2}
  • Children who develop asthma early in life (by age 6)
    • Have evidence of decline in lung function which persists into early adulthood
    • The more severe the symptoms, the more significant the decline
  • Adolescents
    • Majority of persistent wheezers have improvement in symptoms during adolescence
      • Symptoms can reemerge later in adulthood
    • In general, a symptomatic teenager = symptomatic adult

\textsuperscript{1}Am Rev Resp Dis 1992, \textsuperscript{2}JACI 2006
Effect of Interventions on Natural History of Asthma

• While current medical treatments are effective in—
  • Controlling symptoms
  • Preventing exacerbations

• Bottom line is….  
  • Our treatments—
    • Do not prevent underlying severity of asthma
    • Do not alter long-term course$^{1,2,3}$

$^1$NEJM 2000, $^2$NEJM 2006 $^3$EPR3 2007; pg 28
Asthma phenotypes

• Physiologic definition of asthma is relatively nonspecific
  • Airflow limitation during expiration, which is reversible with bronchodilators
• Increasing amount of evidence suggests asthma—
  • Not a single disease
OR
• A single disease that produces widely varying host responses
Asthma phenotypes

- Much about asthma pathophysiology is still unknown
- But, exploration/utilization of current knowledge, hopefully, will translate into more optimized asthma treatment
Asthma phenotypes

1. Eosinophilic
   A. Allergen exacerbated
   B. Idiopathic eosinophilic
   C. Aspirin exacerbated respiratory disease

2. Noneosinophilic
   A. Paucigranulocytic
   B. Neutrophilic

Eosinophilic phenotype

- Lab tests to assess for eosinophilic inflammation
  - Sputum eosinophil count
    - Best predictor of airway eosinophils
    - BUT, is time-consuming and error prone
      - Only performed in experienced centers
  - Peripheral eosinophil count
    - A good predictor of response to Th2-targeted medications—Mepolizumab (Nucala), etc
    - BUT, levels are not specific to asthma and drop with steroid treatment
Eosinophilic phenotype

- Lab tests to assess for eosinophilic inflammation
  - FeNO (Fraction of exhaled Nitric Oxide)
    - Increased FeNO levels correlate with airway eosinophil levels and response to ICS
    - BUT, FeNO levels can be altered by many different factors (age, sex, allergic rhinitis, cigarette smoking) making it less reliable
Eosinophilic asthma phenotype

- Lab tests to assess for eosinophilic inflammation
  - Periostin
    - An extracellular matrix protein, induced by IL-4 and IL-13
    - Better predictor of airway eosinophilia than peripheral eosinophils or FeNO
    - Currently, only available in research facilities
Asthma phenotypes

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Eosinophilic—
Allergen Exacerbated

• Likely most common phenotype
  • 45-88% of asthmatics in recent studies
• Childhood-onset asthma
• Male > Female
• Strong family history of allergies
• More likely to follow a seasonal pattern
• Tend to have more asthma flares with exercise
Eosinophilic—
Allergen Exacerbated

• Positive skin prick tests to—
  • Seasonal allergens (Pollens/molds)
  • Perennial allergens (Animals, dust mites)

• Treatment
  • Tend to respond well to steroids (ICS or OCS)
  • Immunotherapy will improve both allergic rhinitis and asthma symptoms
  • Omalizumab (Xolair) is option for patients ≥ 6 yrs old with perennial allergies (animals, dust mite)
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Eosinophilic—Idiopathic Eosinophilic Asthma

- Less common (10-33% of asthmatics)
- Adult onset
- Female > Male
- Tends to be more severe
- No personal or family history of allergy
  - Negative skin testing
- BUT, have elevated eosinophils (sputum and peripheral) and elevated Th2 cytokines: Interleukin (IL)-4, 5, and 13
  - Take part in eosinophil production pathway
Eosinophilic—Idiopathic Eosinophilic Asthma

- Treatment
  - Somewhat good response to steroids (not as well as allergic asthma)
  - Anti-IL-5 monoclonal antibody therapies
    - Mepolizumab (Nucala)
      - FDA approved in November 2015
      - ≥ 12 yrs of age
    - Resilizumab (Cinqair)
      - FDA approved in April 2016
      - ≥ 18 yrs of age
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Eosinophilic—Asthma Exacerbated Respiratory Disease

Asthma
  +
Chronic rhinosinusitis
  +
Nasal polyps
  +
Aspirin/NSAID sensitivity
(Upper and lower respiratory tract symptoms with aspirin or NSAID use)
Eosinophilic—Asthma Exacerbated Respiratory Disease

- Prevalence: 7% of all asthmatics
- Associated with more severe, refractory asthma
  - Rhinitis typically presents first
  - Patients report a decreased sense of smell
  - Less responsive to steroids (ICS)
- Female > Male
- Age of onset: 30-34 yrs
Eosinophilic—Asthma Exacerbated Respiratory Disease

- Pathophysiology
  - “Pseudoallergic”—Not IgE-mediated
  - Dysregulation of arachidonic acid (AA) metabolism

NORMAL: Aspirin/NSAIDs (COX-1 inhibitors)—block PGE$_2$  
PGE$_2$ blocks 5-LO pathway—leading to decreased leukotrienes (decreased inflammation)

AERD patients:
  - Their PGE$_2$ does not block 5-LO pathway—leading to overproduction of leukotrienes
  - Taking Aspirin/NSAIDs further reduces PGE$_2$ activity, compounding the over-abundance of leukotrienes (severe inflammation)
Eosinophilic—Asthma Exacerbated Respiratory Disease

- **Treatment**
  - Leukotriene-modifying agents
    - LTRAs (montelukast, zafirlukast)
      - Typically used initially, less side effects, monitoring
    - 5-LO inhibitor (zileuton)
      - Used if above fails
      - Tends to be more effective, but must monitor LFTs and interacts with other drugs
  - Avoid all NSAIDs
    - Exclusion: may tolerate COX-2 inh (Celecoxib) and acetaminophen
  - Aspirin desensitization
Asthma phenotypes

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Noneosinophilic asthma phenotype

• Definition: 40-60% neutrophils in induced sputum
  • Elevated Interleukin (IL)-17 cells (Th17)
• More often seen in older adults with more severe asthma
• Do not respond to steroids
Noneosinophilic asthma phenotype

- Its existence is controversial
  - Increased sputum neutrophils also found with—
    - Steroid use
    - Exposure to air pollution
    - Respiratory tract infections
    - Sensitization to aspergillus mold
    - GERD
Asthma phenotypes

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   A. Allergen exacerbated
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   C. Aspirin exacerbated respiratory disease

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   B. Neutrophilic
Noneosinophilic—Paucigranulocytic asthma

- Should it be its own distinct 3rd phenotype?
  - Lacks eosinophils, but does not express IL-17 cells

- Treatment
  - Macrolide antibiotics
  - Methotrexate
  - Phosphodiesterase IV inhibitors
Asthma phenotypes

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Noneosinophilic—Neutrophilic asthma

- Express IL-17 (Th17) cells
- Treatment
  - Macrolide antibiotics
  - Methotrexate
  - Phosphodiesterase IV inhibitors
- IL-17 receptor blocker
  - Brodalimumab
    - Failed phase I trials
    - Future studies not considered
Other Asthma Clinical Presentations

1. Exercise induced bronchospasm
2. Asthma associated with obesity
3. Perimenopausal onset asthma
4. Asthma in pregnancy
Exercise-induced bronchoconstriction (EIB)

- Asthma symptoms during/after exercise are thought to be due to heat and evaporative water loss from the airway
- Exercise-induced asthma (EIA) term is inaccurate—
  - Exercise induces an asthma attack, not asthma.
- More precise term—
  - Exercise-induced bronchoconstriction (EIB)
Exercise-induced bronchoconstriction (EIB)

- Is incorrectly thought of as a unique form of asthma
  - Most asthmatics will develop exercise-induced symptoms if they perform vigorous exercise
  - EIB has also been described in 7-20% of the general non-asthmatic population
Exercise-induced bronchoconstriction (EIB)

- Treatment
  - Pretreat with albuterol
  - Montelukast
    - May be helpful in EIB
  - ICS + LABA
    - May be better than ICS alone
Other Asthma Clinical Presentations

1. Exercise induced bronchospasm
2. Asthma associated with obesity
3. Perimenopausal onset asthma
4. Asthma in pregnancy
Asthma associated with obesity

- Several studies show increase in asthma prevalence in obese patients\(^1\)
- Female > Male
- Patients tend to be more non-allergic
- More likely to be severe and difficult to treat
- Treatment
  - Weight loss is ideal, but controversial— inconsistency in asthma improvement has been seen in studies\(^2\)

Other Asthma Clinical Presentations

1. Exercise induced bronchospasm
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Other Asthma Clinical Presentations

1. Exercise induced bronchospasm
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Asthma in pregnancy

• If ICS needs to be started during pregnancy, budesonide (Pulmicort) is preferred ICS for women with mild/moderate persistent asthma\(^1\)

• However, no evidence exists that shows that other ICSs are unsafe during pregnancy

  • Therefore, patients whose asthma is well controlled before pregnancy, on an ICS other than budesonide, may continue taking that medication

\(^1\) National Asthma Education Prevention Program. Working Group Report: Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment-Update Bethesda, MD 2004. NIH pub 05-3279
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  • Treatment
• Conclusion
Evaluation of Asthma

• Patient should have--
  • Recurring or persistent episodes of symptoms suggestive of asthma
    • Cough
    • SOB
    • Chest tightness
    • Wheezing
  • Evidence of reversible airflow obstruction on spirometry
• Alternative diagnoses excluded
Diagnosis
Use of Spirometry Testing

• By definition, asthma is recurrent symptoms WITH evidence of reversible airflow obstruction

• Spirometry testing (or bronchoprovocation testing) must be used to make an official diagnosis of asthma

• Peak Flow measurements
  • According to the NAEPP/EPR guidelines, peak flow measurement is not an accurate diagnostic tool
  • Used to assess control, response to SABA
Peak Flow in Children

• NAEPP/EPR: peak flow measurement is not an accurate diagnostic tool

• What about children who are too young to perform spirometry testing?
  • Keep in mind that 60% of children who wheeze in first 3 yrs of life may NOT have asthma
    • Could just treat with ICS and/or Albuterol until older and then rule out asthma with spirometry testing
  • Could use peak flow meter to assess for airway hyperreactivity
Peak Flow in Children

- Best of 3 on daily basis at same time of day
  - Establish baseline peak flow measurement
  - $\geq 80\%$ of best baseline is considered normal (GREEN Zone)
- Best of 3 prior when having acute symptoms PRIOR to using Albuterol
- Use Albuterol 2 puffs or 1 ampule via nebulizer
- Wait 15 minutes
- Repeat best of 3 measurements
- If PEF level drops $\leq 80\%$ (YELLOW or RED ZONE), then after Albuterol increased to $> 80\%$
  - Possible evidence of airway hyperreactivity
Quick guide to reading PFTs

**Pulmonary Function Report**

- **Name:** [redacted]
- **ID:** [redacted]
- **Birthdate:** [redacted]
- **Ethnic group:** Caucasian
- **Predicted set:** El Paso-Wang-NHANES III
- **Smoking history:** (no-smoker)

**Diagnosis:**
- **MILD OBSTRUCTIVE PULMONARY IMPAIRMENT.** This is indicated by the finding of a mild reduction in the forced expiratory volume in one second as a % of the forced vital capacity (FVC). The degree of functional impairment reflected by the reduction in forced expiratory volume in the first second (FEV1) is found to be mild. The disproportionately low forced expiratory flow during the middle half of the expiration (FEF 25-75%) suggests the presence of a significant component of small airway obstruction which may evidence a degree of reversibility. This interpretation is valid only upon physician review and signature.

**Site:**

**Physician:** [redacted]

**Effort protocol:** ATS/ERS 2005

**Test date/time:** 04/23/13 12:42:03 PM

**Number of efforts performed:** 3

**Results:**

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<td>FVC (L)</td>
<td>5.25</td>
<td>4.37</td>
<td>4.57</td>
<td>87%</td>
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<td>FEV1 (L)</td>
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<td>FEF 25-75% (L/s)</td>
<td>4.68</td>
<td>3.18</td>
<td>1.89</td>
<td>40%</td>
<td>1.85</td>
<td>39%</td>
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<td>PEFR (L/s)</td>
<td>9.68</td>
<td>7.50</td>
<td>9.06</td>
<td>94%</td>
<td>8.94</td>
<td>92%</td>
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<tr>
<td>Vent (%)</td>
<td>—</td>
<td>—</td>
<td>1.34</td>
<td>—</td>
<td>1.30</td>
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**Test comments:**

- [Graphs and charts showing FVC, FEV1, and other pulmonary function test results]
Acceptability – good test?

• First question when reading spirometry…

• Is it a valid test?

• Demographics correctly entered?

• Effort/reproducibility
Acceptability – good test?

- Evidence of maximal effort
  - Sharp initial peaks
Acceptability – good test?

- Smooth continuous exhalation for at least 6 seconds
  - No coughing (esp in first second) or early glottic closure
Acceptability – good test?

- Obvious end of test
  - No change in volume for $\geq 2$ seconds (PLATEAU)
Acceptability – good test?

• Reproducible efforts
  • 2 best FVCs within 5% and 150ml of each other
Forced Vital Capacity (FVC)

- Measurement of lung volume after taking in a full inspiration and blowing out until only air left in lungs is the residual volume (RV)
- Rapid, forceful, sustained, maximum expiration
- Normal > 80% predicted
**FEV₁**

- Total volume of air blown out in the first second
- Determines severity of airway obstruction
- Normal > 80%

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<td>3.02 68%</td>
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FEV₁ / FVC

- Best measurement of airway obstruction
- Shown as
  - absolute ratio AND % predicted
- ONLY use the absolute ratio
  - NOT % predicted
- Normal FEV1/FVC
  - 8-19 yrs: 0.85
  - 20-39 yrs: 0.80
  - 40-59 yrs: 0.75
  - 60-80 yrs: 0.70
FEF 25-75%

- Rate of air flow during the middle of exhalation
  - “mid-flows”

- Reflects air flow in the peripheral or small airways
  - Less sensitive and specific
  - Not used for diagnosis or assessment of control
    - ≥ 12% rise in FEV1 + FEF25-75 following Albuterol

- Normal > 70%

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PEFR

- Measurement of FLOW rate, not volume
- Primarily central airways
  - FEV1 *more* representative of distal airflow
- Measured in L/sec
- Handheld peak flow meter measured in L/min

\[
\text{PEFR} \times 60 = \text{L/min}
\]
Total Expiration Time (TET)

- Time to completely exhale vital capacity
  - Adults/older children: 6 to 7 seconds
  - Younger children can exhale all of VC in <3 sec

**Volume vs time Curve:**
- Want a plateau (ideal > 2 seconds)
Flow-Volume Curve

• Enable recognition of characteristic patterns of pathology

• Allow recognition of poor effort or mistakes
Flow-Volume Loops: Obstructive Pattern

- "Scooped out" appearance
- Reduced midflows
- Reduced flow-volume slope
- Low overall flows
Diagnosis
Use of Spirometry Testing

• To determine severity of obstruction
  • **First**
    • Is FEV1/FVC ratio reduced (obstructed)?

  • **Second**
    • Is FEV1 reduced or normal?
      • $FEV_1 \geq 80\%$ *(mild)*
      • $FEV_1 > 60\%$ but $< 80\%$ *(moderate)*
      • $FEV_1 < 60\%$ *(severe)*
1. Is FEV1/FVC ratio reduced (obstructed)?
2. Is FEV1 reduced or normal?

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<td>10.38</td>
<td>8.00</td>
<td>7.43 72%</td>
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<tr>
<td>Vext (%)</td>
<td>--</td>
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<td>1.25</td>
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1. FEV1/FVC ratio is obstructed  
   Moderate obstructive pattern
2. FEV1 is < 80%, but >60% (moderate)
Diagnosis
Use of Spirometry Testing

To assess for reversibility of airway obstruction

- **Children**
  - Administer Albuterol 2.5 mg nebulizer (or 2 puffs MDI)
- **Teenagers/Adults**
  - Administer Albuterol 5 mg nebulizer (or 4 puffs MDI)
- Repeat spirometry 15 minutes after completion of neb/MDI treatment
- Reversibility present if—
  - \( \geq 12\% \) rise and 200 mL increase in FEV\(_1\) occurs post-BD
Post-BD Spirometry

- 13% and 470 mL rise in FEV1 post-BD
- Diagnostic of Asthma

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△ indicates change from pre-BD to post-BD.
Evaluation of Asthma Diagnostic Testing

• What if history and symptoms suggestive of asthma, but spirometry normal?
  • Consider the DDx of asthma
  • Consider Allergy or Pulmonology referral
    • Methacholine challenge testing
    • Exercise challenge testing

• A normal spirometry in an asymptomatic asthmatic does not rule out asthma
Evaluation of Asthma Diagnostic Testing

- Methacholine Challenge Test
  - Drop in FEV$_1$ $\geq$ 20%
  - $\geq$ 5 yrs of age (if they can tolerate)

- Exercise Challenge Test
  - Treadmill or outdoors
  - Drop in FEV$_1$ $\geq$ 15%
  - Any age (if they can tolerate)
Differential diagnostic possibilities for asthma

**Infants and children**

Upper airway diseases
- Allergic rhinitis and sinusitis

Obstructions involving large airways
- Foreign body in trachea or bronchus
- Vocal cord dysfunction (VCD)
- Vascular rings or laryngeal webs
- Laryngotracheomalacia, tracheal stenosis, or bronchostenosis
- Enlarged lymph nodes or tumor

Obstructions involving small airways
- Viral bronchiolitis or obliterative bronchiolitis
- Cystic fibrosis
- Bronchopulmonary dysplasia
- Heart disease

**Other causes**
- Recurrent cough not due to asthma
- Aspiration from swallowing mechanism dysfunction or gastroesophageal reflux

**Adults**
- COPD (eg, chronic bronchitis or emphysema)
- Congestive heart failure
- Pulmonary embolism
- Mechanical obstruction of the airways (benign and malignant tumors)
- Pulmonary infiltration with eosinophilia
- Cough secondary to drugs (eg, angiotensin-converting enzyme inhibitors)
- VCD
Paradoxical Vocal Fold Motion (Vocal Cord Dysfunction)

- Episodic unintentional adduction of the vocal folds on inspiration
- Patients describe throat tightness, a choking sensation, dysphonia, and cough
- On PE, wheezing, stridor, and apparent upper airway obstruction observed
- Symptoms may occur spontaneously or with exercise, irritant exposure, or anxiety
- Albuterol does not help
Paradoxical Vocal Fold Motion (Vocal Cord Dysfunction)

• Diagnosis
  • Flattening of inspiratory loop on spirometry
  • Visualization of abnormal adduction of the true vocal folds on rhinoscopy
  • Videostroboscopy
Paradoxical Vocal Fold Motion (Vocal Cord Dysfunction)

- **Treatment**
  - Acute management of stridor/airway obstruction
    - Reassurance
    - CPAP
    - Heliox
  - Long-term
    - Speech therapy treatment exercises
      - Breathing retraining
      - Rescue breathing
      - Relaxation techniques
Outline

• Asthma
  • Definition
  • Risk factors
  • Natural history
  • Asthma phenotypes
  • Evaluation
  • Diagnosis
  • Mimickers/Comorbidities of Asthma
  • Treatment

• Conclusion
Treatment Basics

• Once diagnosis of asthma made, to initiate treatment, must assess asthma severity
  • According to the NHLBI/EPR3 guidelines
• Key point:
  • Assign to the MOST SEVERE category in which any feature occurs
Assign Severity

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity ≥12 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Persistent</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Mild</td>
</tr>
<tr>
<td>≤2 days/week</td>
<td>Moderate</td>
</tr>
<tr>
<td>&gt;2 days/week but not daily</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>Severe</td>
</tr>
<tr>
<td>≤2x/month</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Short-acting</td>
<td>Daily</td>
</tr>
<tr>
<td>β₂-agonist use for</td>
<td>Several times per day</td>
</tr>
<tr>
<td>symptom control (not</td>
<td></td>
</tr>
<tr>
<td>prevention of EIB)</td>
<td></td>
</tr>
<tr>
<td>Interference</td>
<td>None</td>
</tr>
<tr>
<td>with normal</td>
<td>Minor limitation</td>
</tr>
<tr>
<td>activity</td>
<td>Some limitation</td>
</tr>
<tr>
<td></td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

| Normal FEV₁/FVC:       | Lung function                                     |
| 8–19 yr 85%           | Normal FEV₁ between exacerbations                 |
| 20–39 yr 80%          | FEV₁ >80% predicted                               |
| 40–59 yr 75%          | FEV₁/FVC normal                                   |
| 60–80 yr 70%          |                                                   |

| Risk                   | Exacerbations requiring oral systemic corticosteroids |
|                        | 0–1/year (see note)                                  |
|                        | ≥2/year (see note)                                   |

Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV₁.

<table>
<thead>
<tr>
<th>Recommended Step for Initiating Treatment</th>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3 and consider short course of oral systemic corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
#1 Look at the rules of “2”s

<table>
<thead>
<tr>
<th></th>
<th>Intermittent</th>
<th>Mild</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2x/month</td>
<td>3–4x/month</td>
<td>&gt;1x/week but not nightly</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
<td>&gt;2 days/week but not daily, and not more than 1x on any day</td>
<td>Daily</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extremely limited</td>
</tr>
</tbody>
</table>

- Assign patient to the **MOST SEVERE** category in which any feature occurs
- So far, patient above meets **MILD PERSISTENT ASTHMA** category
#2

Look at spirometry values

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td></td>
<td>Normal FEV₁/FVC:</td>
</tr>
<tr>
<td>Normal</td>
<td>8–19 yr</td>
</tr>
<tr>
<td>Impairment</td>
<td>20–39 yr</td>
</tr>
<tr>
<td>Normal</td>
<td>40–59 yr</td>
</tr>
<tr>
<td>Impairment</td>
<td>60–80 yr</td>
</tr>
</tbody>
</table>

Lung function

- Normal FEV₁ between exacerbations
- FEV₁ > 80% predicted
- FEV₁/FVC normal
- FEV₁ > 80% predicted
- FEV₁/FVC normal
- FEV₁ > 60% but < 80% predicted
- FEV₁/FVC reduced 5%
- FEV₁ < 60% predicted
- FEV₁/FVC reduced > 5%
### Spirometry

<table>
<thead>
<tr>
<th>Results</th>
<th>Predicted</th>
<th>LLN</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (L)</td>
<td>5.74</td>
<td>4.78</td>
<td>01/14/13 06:45:44 AM</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>4.75</td>
<td>3.94</td>
<td>3.58</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.83</td>
<td>0.74</td>
<td>0.65</td>
</tr>
<tr>
<td>FEF25-75% (L/s)</td>
<td>4.92</td>
<td>3.27</td>
<td>2.35</td>
</tr>
<tr>
<td>PEFR (L/s)</td>
<td>10.38</td>
<td>8.00</td>
<td>7.43</td>
</tr>
<tr>
<td>Vext (%)</td>
<td>--</td>
<td>--</td>
<td>1.25</td>
</tr>
</tbody>
</table>

- FEV1 is <80%
- FEV1/FVC ratio is reduced > 5% (regardless of age of patient)
Looking at spirometry values

### Impairment

<table>
<thead>
<tr>
<th>Normal FEV\textsubscript{i}/FVC</th>
<th>8–19 yr</th>
<th>85%</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–39 yr</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>40–59 yr</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>60–80 yr</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung function</th>
<th>Intermittent</th>
<th>Persistent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Moderate</td>
</tr>
<tr>
<td>Normal FEV\textsubscript{i} between exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{i} &gt; 80% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{i}/FVC normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{i} &gt; 80% predicted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV\textsubscript{i}/FVC normal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Mild**: FEV\textsubscript{i} > 60% but < 80% predicted
- **Moderate**: FEV\textsubscript{i} < 60% predicted
- **Severe**: FEV\textsubscript{i}/FVC reduced > 5%

Now, patient meets **SEVERE PERSISTENT ASTHMA** category
• Patient has never been treated with oral steroids.
#4 Assess what treatment step to start patient on

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (≥12 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Intermittent</strong></td>
</tr>
<tr>
<td></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td></td>
<td>≤2x/month</td>
</tr>
<tr>
<td></td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Impairment</td>
<td>None</td>
</tr>
<tr>
<td>Normal FEV₁/FVC:</td>
<td></td>
</tr>
<tr>
<td>8–19 yr</td>
<td>85%</td>
</tr>
<tr>
<td>20–39 yr</td>
<td>80%</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>75%</td>
</tr>
<tr>
<td>60–80 yr</td>
<td>70%</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/FVC normal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exacerbations requiring oral systemic corticosteroids</th>
<th>0–1/year (see note)</th>
<th>≥2/year (see note)</th>
</tr>
</thead>
</table>

**Risk**

Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV₁.

**Recommended Step for Initiating Treatment**

(See figure 4–5 for treatment steps.)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4 or 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td></td>
<td>and consider short course of oral systemic corticosteroids</td>
<td></td>
</tr>
</tbody>
</table>
Options:
1. Medium or high dose ICS + LABA
2. Consider adding Montelukast
Consider allergy shots if pt has allergic triggers
• BUT, asthma must be well controlled first
Treatment Basics

- Once patient’s asthma symptoms are under control
  - Keep patient on that dose dose for 3-6 months
    - Then consider **stepping down therapy**
      - If on 2 puffs BID
        - Decrease to 1 puff BID
  - Continue stepping down again in 3-6 months
<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma Control (≥12 years of age)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impairment</strong></td>
<td><strong>Well Controlled</strong></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2 x/month</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting beta₂-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/personal best</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td></td>
</tr>
<tr>
<td>ATAQ</td>
<td>0</td>
</tr>
<tr>
<td>ACQ</td>
<td>≤0.75&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACT</td>
<td>≥20</td>
</tr>
<tr>
<td>Risk</td>
<td><strong>Not Well Controlled</strong></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Consider severity and interval since last exacerbation</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>&gt;2/year (see note)</td>
</tr>
<tr>
<td></td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
</tr>
</tbody>
</table>

### Recommended Action for Treatment

(see figure 4–5 for treatment steps)

- Maintain current step.
- Regular followups every 1–6 months to maintain control.
- Consider step down if well controlled for at least 3 months.
- Step up 1 step and Reevaluate in 2–5 weeks.
- For side effects, consider alternative treatment options.

- Consider short course of oral systemic corticosteroids,
- Step up 1–2 steps, and Reevaluate in 2 weeks.
- For side effects, consider alternative treatment options.
Treatment

• Inhaled corticosteroids (ICS)
  • Examples
    • Beclomethasone HFA (QVAR®)
      • ≥ 5 yrs old
    • Fluticasone HFA (Flovent®)
      • ≥ 4 yrs old
    • Mometasone DPI (Asmanex®)
      • ≥ 4 yrs old
      • Contains milk protein
Treatment

• Inhaled corticosteroids (ICS)
  • Examples
    • Budesonide (Pulmicort®) respules
      • Any age
    • Budesonide (Pulmicort®) flexihaler
      • ≥ 6 yrs old
      • Contains milk protein
    • Flunisolide (Aerobid®)
      • ≥ 6 yrs old
    • Ciclesonide (Alvesco®)
    • Fluticasone furoate (Arnuity Ellipta®)
Inhaled corticosteroids (ICS) Side Effects

• Thrush, dysphonia/hoarseness
• For prevention:
  • Recommend a spacer (if applicable) and demonstrate use
  • Rinse mouth after each use
  • Use lowest dose necessary to control asthma
  • Consider Ciclesonide (Alvesco®)
Ciclesonide (Alvesco®)

- Smallest particle size
- Least dysphonia/voice hoarseness side effect

- ≥ 12 yrs of age
- 80 mcg or 160 mcg canisters
- Starting dose: 1 puff BID
Inhaled corticosteroids (ICS) Side Effects

• Height
  • Childhood Asthma Mgmt Program (CAMP) study
    • Adult height measured at 25.9± 2.7 yrs
    • CAMP study: 5-13 year old asthmatics received 200 mcg budesonide bid vs nedocromil vs placebo
    • Mean adult height was 1.2 cm lower in budesonide group than placebo (p=0.001)
    • Mean adult height was 0.2 cm lower in nedocromil group than placebo (p=0.61)
  • Height reduction was seen 2 yrs after onset of ICS.
  • Did not get progress to even more loss in height

NEJM 367:10 904-912 (2012)
Fluticasone furoate (Arnuity Ellipta®)

- ICS monotherapy
- ≥ 12 yrs of age
- 100 mcg, 200 mcg DPI
- 1 INH once daily dosing
- Inactive ingredients: contains milk proteins
Treatment

- Combination medications (ICS + LABA)
  - Examples
    - Fluticasone/salmeterol DPI/HFA (Advair®)
      - Diskus ≥ 4 yrs old, contains milk protein
      - HFA ≥ 12 yrs old
    - Budesonide/formoterol HFA (Symbicort®)
      - ≥ 12 yrs old
      - Off-label ≥ 5 yrs old
Treatment

• Combination medications (ICS + LABA)
  • Examples
    • Mometasone furoate/formoterol fumarate dihydrate (Dulera®)
      • ≥ 12 yrs old
    • Fluticasone furoate/vilanterol (Breo Ellipta®)
LABA Side Effects\textsuperscript{1-3}

- SMART trial (Salmeterol Multicenter Asthma Research Trial)
  - Published 2006
  - A small, but significant increase in respiratory-related deaths of African Americans using serevent (LABA monotherapy) vs placebo.
  - Unknown if genetics/patient behaviors (delay in seeking care) were factors
- 2010, the FDA required the black box warning emphasizing risk of LABA monotherapy
- Also recommended trial on ICS alone before moving to ICS/LABA
- However, did not answer whether combining ICS with LABA reduces the LABA risk above
  - Study to answer this question to be completed in 2017

\textsuperscript{1}Chest 2006;129:15-26
\textsuperscript{2}NEJM 2010; 362:13
\textsuperscript{3}JACI 2012;129:1274-9
Fluticasone furoate/vilanterol (Breo Ellipta®)

- Combination medication (ICS + LABA)
- ≥ 18 yrs of age
- 100 mcg/25 mcg, 200 mcg/25 mcg DPI
- 1 INH once daily dosing
- Inactive ingredients: Contains milk proteins
Treatment
Leukotriene Modifiers

- Leukotriene reuptake antagonists (LTRAs)
  - Used as monotherapy in children, EIB
  - Add-on therapy for allergic asthma, EIB, AERD

- Montelukast (Singulair)
  - ≥ 6 months
  - Mostly well-tolerated
    - Mood changes, rare pulmonary eosinophilia risk

- Zafirlukast (Accolate)
  - ≥ 5 yrs of age
  - Similar side effect risk
Leukotriene Modifiers

- 5-LO inhibitor
  - Zileuton (Zyflo)
    - "Upstream"—Blocks production of all leukotrienes
    - ≥ 12 yrs old
    - Must take QID
    - Risk of possible liver toxicity
Treatment
Methylxanthines (Theophylline)

• “Old school”, but is option for severe asthmatics

Methylxanthines
Theophylline, sustained-release tablets and capsules

Indications
- Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma.

Mechanisms
- **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism.
- May affect eosinophilic infiltration into bronchial mucosa as well as decreases T-lymphocyte numbers in epithelium.
- Increases diaphragm contractility and mucociliary clearance.

- Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVT), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia.
- Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, increase in hyperactivity in some children, difficulty in urination in elderly males who have prostatism.

- Maintain steady-state serum concentrations between 5 and 15 mcg/mL. Routine serum concentration monitoring is essential due to significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by numerous factors which can produce significant changes in steady-state serum theophylline concentrations.
- Patients should be told to discontinue if they experience toxicity.
- Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. Serum concentration monitoring is mandatory.
Treatment
Tiotropium (Spiriva Respimat)

• Results from 2 randomized trials\(^1\):
  • Add-on tiotropium significantly increased time to next severe exacerbation and modestly increased FEV1

• Anti-cholinergic
• Add-on therapy
• \(\geq 12\) yrs of age
• Spiriva Respimat 1.25 mcg/actuation—2 INH daily
  • May take up to 4 to 8 weeks to achieve max benefit
  • Side effects: urinary retention, increased glaucoma pressure

1. NEJM 2012;367:1198-207
Treatment
Omalizumab (Xolair)

- Recombinant humanized monoclonal anti-IgE antibody
  - Binds IgE at same Fc site as FceR1
    - Directly reduces circulating IgE levels
    - Indirectly causes downregulation of high affinity IgE receptors
- Indications:
  - ≥ 6 yrs of age
  - Moderate/severe persistent asthma patients
  - Eosinophilic asthma—Allergen exacerbated
    - (+) skin testing or serum IgE testing (Immunocap) to perennial allergens (animals, dust mites)
Treatment
Omalizumab (Xolair)

• Results in:
  • Decrease in asthma exacerbations and hospitalizations
  • Decreased symptom scores

• Dose determined by total IgE x body weight (kg)
  • SQ injections every 2-4 weeks

• Side effects: low risk of anaphylaxis, questionable increase in malignancy, CAD/stroke
Treatment
Mepolizumab (Nucala)

- Monoclonal anti-IL-5 antibody
  - Approved in Nov 2015
  - Reduced asthma exacerbations, improved QOL
- For Idiopathic eosinophilic asthma phenotype
  - Add-on, maintenance treatment for severe asthma patients with peripheral eosinophil count ≥ 150/microl
- ≥ 12 yrs of age
- 100 mg SQ every 4 weeks
- Side effects: Increased risk of varicella-zoster (shingles)

Treatment
Reslizumab (Cinqair)

- Monoclonal anti-IL-5 antibody
  - Approved in Apr 2016
  - Reduced asthma exacerbations, improved QOL\(^1\)
- For Idiopathic eosinophilic asthma phenotype
  - Add-on, maintenance treatment for severe asthma patients with peripheral eosinophil count ≥ 400/microl
- ≥ 18 yrs of age
- 3 mg/kg IV every 4 weeks
- Side effects: Anaphylaxis, mouth/throat pain

 Bronchial Thermoplasty

- Technique of applying heat (65° C) via controlled radiofrequency waves to airways during bronchoscopy
- 3 separate treatment about three weeks apart
- Reduces the increased mass of airway smooth muscle associated with asthma
- Indications:
  - ≥ 18 yrs of age
  - Severe asthma, on oral steroids
- Side effects/risk: damage to airway/fibrosis
Treatment
Vitamin D supplement

- CAMP study participants with decreased Vit D (< 20ng/mL) had worse lung function than those with higher levels\(^1\)

- Check Vit D 25 (OH) level

- Supplement with Vit D3 (cholecalciferol) per level recommendations

\(^1\)American journal of respiratory and critical care medicine. 186(6):508-13, 2012
Asthma Action Plan (AAP)

- Written asthma action plans for children
  - Cochrane Review 2009
  - Symptom based vs Peak-flow based AAP
  - Study did not compare AAP vs no AAP when all other co-interventions were kept similar
    - 2001 study of 89 asthma deaths compared to controls demonstrated 70% decreased risk of death with AAP*
  - Symptom based AAP had lower risk of exacerbations requiring acute care visit
  - Peak Flow based AAP had decreased in symptomatic days/week
  - No difference in oral steroids, admission, school absence, lung function, symptom scores, QOL

*Am J Respir Crit Care Med. 2001 Jan;163(1):12-8
Treatment Immunotherapy

• Randomized controlled studies\(^1\)-\(^4\) showed that allergen immunotherapy prevents the development of asthma in younger subjects with allergic rhinitis

Conclusions

• Increasing evidence that asthma is a compilation of different phenotypes, that are still poorly understood

• Allergy exacerbated asthma is most common form in children
  • 40% of patients with allergic rhinitis have asthma, 80% of asthmatics have allergies
  • Need for allergy testing and allergy treatment, including immunotherapy

• Evidence of airway hyperresponsiveness and chronicity of symptoms are key to diagnosis of asthma
  • >12% rise and 200 mL increase in FEV\textsubscript{1} diagnostic of reversible airway obstruction
Questions?