Please complete the preassessment located in your handout before the program begins.

Faculty and Disclosures

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Learning Objectives

Upon completion of this activity, learners should be better able to:

• Differentiate between mild to moderate asthma and severe asthma
• Recognize the characteristics of difficult-to-control severe asthma vs treatment-refractory severe asthma and when to refer to a specialist
• Individualize maintenance strategies for patients with pediatric asthma based on current guidelines and disease severity
Asthma Epidemiology

• Most common chronic lung disease of childhood
• Approximately 6,000,000 children in the US¹
• 2013: children with asthma ages 5 to 17 missed 13.8 million days of school per year (2.6 days/child)²
• 2016: half of all children with asthma had at least one asthma attack²


Imagine That…

• You are 8 years old
• You feel a weight on your chest every day – like someone wrapped it tight with duct tape
• Every breath takes an effort
• Your lungs are filled with rubber-cement–like mucus that is nearly impossible to clear out of your airways
• You wake up every night, gasping for air
• Your parents worry that you might not live to become an adult
Mild and Moderate Asthma

**Option A (GINA):** Retrospective assessment of level of treatment required to control symptoms and exacerbations

- **Mild asthma**
  - Well-controlled with PRN albuterol or low-dose inhaled corticosteroid
- **Moderate asthma**
  - Well-controlled with low-dose ICS/LABA

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist.


Mild and Moderate Asthma (cont’d)

**Option B (NHLBI):** Classification of severity at initial visit. Subsequent visits focus on control.

- **Mild asthma**
  - Impairments:
    - Symptoms: > 2 days/week (not daily)
    - Albuterol: > 2 days/week (not daily)
    - Nighttime awakenings: 3-4 times/month
    - Lung function: FEV1% predicted > 80%
  - Risk:
    - > 2 exacerbations/year requiring oral steroids
- **Moderate asthma**
  - Impairments:
    - Symptoms: daily
    - Albuterol: daily
    - Nighttime awakenings: > 1 occurrence/week but not nightly
    - Lung function: FEV1% predicted 60%-80%
  - Risk:
    - > 2 exacerbations/year requiring oral steroids

FEV1, forced expiratory volume in one second.

What Is Severe Asthma?

- **GINA classification**
  - Steps 4-5 (high-dose ICS + LABA or leukotriene modifier) to achieve control
- **Systemic corticosteroids ≥ 50% of previous year to achieve control**
- **Remains uncontrolled despite aggressive therapy**

Uncontrolled Asthma in Children ≥ 6 Years

- **Poor symptom control**
  - ACQ score > 1.5
  - ACT score < 20
- **Frequent, severe exacerbations**
  - 2 or more burst systemic steroids in the previous year
  - Serious exacerbations requiring:
    - At least one hospitalization or PICU stay
    - Mechanical ventilation in the previous year
- **Airflow limitation**
  - FEV1 < 80% after bronchodilator

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; PICU, pediatric intensive care unit.
Key Questions

• Is the patient taking the medication?
• Is the patient using the medication correctly?
• Is the patient on the correct medication?
• Have all triggers been identified and removed?
• Is it really asthma?

Strengths

- Guidelines
- Improved outcomes
- Research
- New drug therapies

Opportunities

- Environmental control
- Evaluation tools
- School nurses
- Consistent follow-up

Breathing Well

Weaknesses

- Incurable disease
- Adherence
- Triggers
- Inhaler technique
- Guideline implementation

Threats

- Missed diagnosis
- Side-effect concerns
- Respiratory viruses
- Medication cost
- Inconsistent follow-up
Current Asthma Guidelines

- National Heart, Lung, and Blood Institute (NHLBI)
  - Updated August 2007
  - Medication update 2011

- GINA
  - Updated 2017
The Control-Based Asthma Management Cycle

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

Asthma medications
Non-pharmacological strategies
Treat modifiable risk factors


Stepwise Management of Asthma

GINA Assessment of Asthma Control

A. Symptom control

- **In the past 4 weeks, has the patient had:**
  - Daytime asthma symptoms more than twice a week? **Yes** / **No**
  - Any night waking due to asthma? **Yes** / **No**
  - Reliever needed for symptoms* more than twice a week? **Yes** / **No**
  - Any activity limitation due to asthma? **Yes** / **No**

<table>
<thead>
<tr>
<th>Level of asthma symptom control</th>
<th>Well-controlled</th>
<th>Partially controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>None of these</td>
<td>1-2 of these</td>
<td>3-4 of these</td>
<td></td>
</tr>
</tbody>
</table>

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 patient's personal best, then periodically for ongoing risk assessment

**Assess patient's risks for:**
- Exacerbations
- Fixed airflow limitation
- Medication side-effects


Decline in Asthma Attacks, 2001-2016

National Health Interview Survey for children aged 0 to 17 years

Improved Outcomes in Severe Asthma

<table>
<thead>
<tr>
<th></th>
<th>1993-1997* (n=65)</th>
<th>2003-2007* (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic oral steroids</td>
<td>51%</td>
<td>28%</td>
</tr>
<tr>
<td>FEV1%</td>
<td>76%</td>
<td>84%</td>
</tr>
<tr>
<td>Albuterol inhalations/week</td>
<td>71</td>
<td>33</td>
</tr>
<tr>
<td>Leukotriene antagonist</td>
<td>0</td>
<td>76%</td>
</tr>
<tr>
<td>Combination LABA/ 2nd generation inhaled steroid</td>
<td>0</td>
<td>66%</td>
</tr>
</tbody>
</table>

*Comparison of two pediatric cohorts evaluated at National Jewish Health.


Diminishing Returns With High-Dose Inhaled Steroid

Combined ICS + LABA

- Improved lung function
- Less albuterol use compared with same ICS dose
- Compared with higher ICS dose
  - 1.2 cm more in growth over one year
  - No difference in control of asthma symptoms
- No difference in number of exacerbations requiring oral steroids
- No increase in serious side effects


Anticholinergics

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism</th>
<th>Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>Moderate to severe disease</td>
<td>≥ 6 years</td>
<td>Increased FEV1 in children with moderate asthma</td>
</tr>
<tr>
<td></td>
<td>Binds to muscarinic receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bronchodilator effect</td>
<td></td>
<td>No significant change in FEV1 in 12- to 17-year-old children with severe</td>
</tr>
<tr>
<td></td>
<td>Long-acting (once-daily dosing)</td>
<td></td>
<td>asthma on ICS + at least one additional controller</td>
</tr>
</tbody>
</table>

Potential side effects: paradoxical bronchospasm, pharyngitis, sinusitis, bronchitis, and headache

Precision Medicine

**Biologic Targeting IgE**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism</th>
<th>Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Omalizumab</strong></td>
<td>Binds to free IgE Fc receptor</td>
<td>≥ 6 years</td>
<td><strong>Decreases:</strong></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td></td>
<td></td>
<td>• Exacerbations</td>
</tr>
<tr>
<td>disease +</td>
<td></td>
<td></td>
<td>• Symptoms</td>
</tr>
<tr>
<td>Sensitization to</td>
<td></td>
<td></td>
<td>• ICS dose</td>
</tr>
<tr>
<td>perennial allergen</td>
<td></td>
<td></td>
<td>• Seasonal asthma</td>
</tr>
</tbody>
</table>

**Potential side effects:** injection-site reactions, respiratory infections

Fc, fragment crystallizable; IgE, immunoglobulin E; QOL, quality of life.

Biologic Targeting Eosinophils

<table>
<thead>
<tr>
<th>Indication</th>
<th>Mechanism</th>
<th>Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benralizumab¹</td>
<td>Anti-IL-5</td>
<td>≥ 12 years</td>
<td>Decreases: Exacerbations, Symptoms, OCS dose</td>
</tr>
<tr>
<td>Severe eosinophilic asthma</td>
<td>• Binds to IL-5Rα receptor and Fcγ receptor NK cells</td>
<td></td>
<td>Increases: FEV1</td>
</tr>
<tr>
<td>Mepolizumab²,³</td>
<td>Anti-IL-5</td>
<td>≥ 12 years</td>
<td>Decreases: Exacerbations, Symptoms, OCS dose</td>
</tr>
<tr>
<td>Severe eosinophilic asthma</td>
<td>• Blocks IL-5 binding to eosinophils</td>
<td></td>
<td>Increases: FEV1</td>
</tr>
</tbody>
</table>

Potential side effects: common cold symptoms, headaches, fever, upper abdominal pain, pharyngitis, ear discomfort, intestinal infection causing abdominal pain, nausea and vomiting, and nosebleeds

IL, interleukin; OCS, oral corticosteroid.
No Curative Treatments

Parents and children move through gradual process from knowledge to acceptance at own pace


Chronic Airway Remodeling

BM, basement membrane; BV, blood vessel; EP, epithelium; SM, smooth muscle.
Adherence

- 4-year study – Childhood Asthma Management Program (CAMP)
- Measurements
  - Subjective: diary cards
  - Objective: dose counter inhaler


Objective Adherence Much Lower Than Self-Reported Adherence

Inhaler Technique

- Prevalence of correct technique only 31%¹
- Appropriate age for inhaler devices²

<table>
<thead>
<tr>
<th>Age</th>
<th>Device</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 years</td>
<td>MDI: spacer + mask</td>
<td>Nebulizer if intolerant MDI</td>
</tr>
<tr>
<td>&gt; 3 years</td>
<td>MDI: spacer + mask</td>
<td>Consider mouthpiece</td>
</tr>
<tr>
<td>&gt; 5-6 years</td>
<td>Dry powder</td>
<td>Evaluate patient for readiness</td>
</tr>
</tbody>
</table>

**Clinical Pearl:** Include reminder in written asthma plan to bring medications and spacer to each visit

MDI, metered-dose inhaler.
Evaluation Tools

- History
  - Important tool
  - Reflects patient’s experience of disease and impact on QOL

- Spirometry
  - Supports diagnosis
  - Important in assessing response to changes in therapy and exacerbations

- Positive test for airway reactivity:
  - Post-bronchodilator FEV1% change > 12% or 200 mL
  - > 8% likely significant in children


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Typical Spirometric Tracings

Asthma Control Questionnaires

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Recall Window</th>
<th>Number of Questions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRACK</td>
<td>0-5 years</td>
<td>1-12 months</td>
<td>5</td>
<td>Includes number of oral steroid courses</td>
</tr>
<tr>
<td>C-ACT</td>
<td>4-11 years</td>
<td>4 weeks</td>
<td>4 by child</td>
<td>Children report lower control</td>
</tr>
<tr>
<td>CASI</td>
<td>&gt; 6 years</td>
<td>2 weeks</td>
<td>5</td>
<td>Includes: FEV1% Medication level Number of exacerbations</td>
</tr>
<tr>
<td>ACQ</td>
<td>&gt; 12 years</td>
<td>1 week</td>
<td>6 + FEV1%</td>
<td></td>
</tr>
<tr>
<td>ACT</td>
<td>&gt; 12 years</td>
<td>4 weeks</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

C-ACT, Childhood Asthma Control Test; CASI, Composite Asthma Severity Index; TRACK, Test for Respiratory and Asthma Control in Kids.

HEPA Air Filters Might Reduce Some Triggers

Indoor Triggers

Preventing Severe Asthma Exacerbations

- Kids screened for dust mite sensitivity after asthma attacks in ER
- 284 sensitized kids randomized
- Outcome: Asthma attacks over 12 months
  - ER visits, hospitalization, or oral steroids

ER, emergency room
Dust Mite-Proof Bedding


45% Lower Risk of ER Visits

Fewer Severe Exacerbations

Hospital Attendance With Asthma Exacerbation

Randomization

Percentage

Active  Placebo

29.3  41.5

P = .047


Decreasing Pet Allergens

- Takes 20 to 24 weeks to reduce cat allergen after removing the animal from home

- Washing pets not effective in decreasing allergens
  - Cats – washing benefits not sustained beyond 1 week
  - Dogs – benefits only sustained if dog washed twice a week

Hypoallergenic Dogs

No difference in airborne antigen between hypoallergenic and regular breeds

Humidifiers

- South Korea: cluster of severe lung disease due to humidifier disinfectant
- No evidence for benefit in asthma
- Can promote mold growth

School-Based Administration of ICSs

- 48 urban students on Medicaid (grades K-8)
- Randomized controlled trial
- 60-day treatment period
- Intervention group
  - 92% received morning ICS at school
  - Decrease in asthma symptoms
  - More sleep
- Despite improvements in intervention group, parents in control group reported same number of ICS treatments, suggesting parental over-reporting


**Strengths**
- Guidelines
- Improved outcomes
- Research
- New drug therapies

**Opportunities**
- Environmental control
- Evaluation tools
- School nurses
- Consistent follow-up

**Weaknesses**
- Incurable disease
- Adherence
- Triggers
- Inhaler technique
- Guideline implementation

**Threats**
- Missed diagnosis
- Side-effect concerns
- Respiratory viruses
- Medication cost
- Inconsistent follow-up

Breathing Well
Red Flags for Missed Diagnosis

- No response to standard asthma therapy
- Chronic productive cough
- Poor weight gain and growth
- Recurrent pneumonia
- Chronic sinusitis
- Sudden onset

Expert Opinion.

Normal and Abnormal Flow-Volume Loop

Normal flow-volume loop

Inspiratory flow-volume loop limitation as seen in vocal cord dysfunction

Vocal Cord Dysfunction

- Poor response to standard asthma therapy
- Acute onset and resolution
- Symptoms disappear during sleep
- Patients often point to throat when asked to locate tightness


Hilar Adenopathy From *Mycobacterium Avium*
Ciliary Dyskinesia

Bronchiectasis
Aberrant Right Subclavian Artery

Foreign Body
Foreign Body

Side Effects of ICSs

- **Local**
  - Oral candidiasis
    - Higher risk with high-dose ICSs
    - Preventable with mouth rinsing immediately after dose

- **Systemic**
  - Growth suppression
    - Effect on final adult height likely negligible
      (1 cm to 0.7% total height)
  - Adrenal suppression
    - Children on moderate- to high-dose ICSs at highest risk

**Clinical Pearl:** Asthma control should be periodically evaluated to determine if dose can be reduced

Clinical Pearl: Exacerbations

- No data supporting increase of inhaled steroids to treat asthma exacerbations
- Increasing inhaled steroids may be associated with diminished linear growth


Medication Costs

- Asthma medications are expensive
  - Combination ICS/LABA: $400-$600/month
- Inconsistent drug coverage between insurance plans
- High drug copays

Reducing Inconsistent Follow-Up

- Partner with parents
- Pay attention to parents' concerns
- Explore barriers to consistent follow-up
  - Health literacy (12% of adults are proficient)
  - Transportation
  - Taking time off work
  - Not understanding why follow-up needed
  - Benefits and goals of therapy not clear
- Population management
  - Patient registry to proactively manage patients

Expert Opinion.

When to Refer to a Pulmonary Specialist

- Need for ≥ step 4 level therapy
- Not responding to standard asthma therapy
- Atypical presentation and diagnosis not clear
- High-risk patients
  - History of hospital admissions
- Need for parent and patient education
The Control-Based Asthma Management Cycle


Strengths
- Guidelines
- Improved outcomes
- Research
- New drug therapies

Opportunities
- Environmental control
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Weaknesses
- Incurable disease
- Adherence
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- Guideline implementation

Threats
- Missed diagnosis
- Side-effect concerns
- Respiratory viruses
- Medication cost
- Inconsistent follow-up

Breathing Well
Take-Home Messages

- Proactively manage difficult-to-control asthma with recurring assessments, treatment adjustments, and review of response
- If patients don’t respond to therapies, systematically explore for barriers, triggers, adherence, and consider different diagnosis
- Newer therapeutics are targeted to specific asthma phenotypes
- Acknowledge patient’s difficulty accepting the chronic illness

Questions?
Thank You

Please complete the postassessment and evaluation located in your meeting handout.