Meeting the Challenge of Asthma

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Challenges of Modern Asthma Care

- Minimize symptoms/maximize function
- Prevent asthma attacks
- Minimize medication side-effects

Lecture Outline

I. Defining asthma control
II. Achieving asthma control: A five-point plan
   A. Making the correct diagnosis
   B. Modifying environmental inciters
   C. Medications to control asthma
   D. Plan for dealing with asthmatic attacks
   E. Specialist consultation

Additional Challenges of Modern Asthma Care

- Equitable distribution of care throughout society
- Availability of low-cost (generic) medications
- Prevention of decline in lung function over time

Presenter Disclosure Information

The following relationships exist related to this presentation:

► Christopher Fanta, MD: No financial relationships to disclose.

Off-Label/Investigational Discussion

► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Staging Asthma Severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Daytime Symptoms</th>
<th>Nighttime Symptoms</th>
<th>Lung Function (FEV1 or PEFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>&lt;2 days/wk</td>
<td>&lt;2 nights/mo.</td>
<td>≥80%</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>3-6 days/wk</td>
<td>3-4 nights/mo.</td>
<td>≥80%</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily</td>
<td>≥5 nights/mo.</td>
<td>&gt;60 - &lt;80%</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual</td>
<td>Frequent</td>
<td>&lt;60%</td>
</tr>
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Assessing Asthma Control

Two “Domains”:
- Current impairment
- Symptoms (daytime, nighttime, and frequency of use of rescue bronchodilator)
- Exercise limitation
- Lung function
- Future risk
- More than 1 oral steroid course in last year

Asthma Control Test

Well-controlled asthma: >20

Achieving Asthma Control

The Five-Point Plan:
A. Making the correct diagnosis
B. Modifying environmental inciters
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Establishing the Correct Diagnosis

- Characteristic history
  - episodic symptoms
  - characteristic triggers
  - characteristic response to medications
- Characteristic examination
  - diffuse musical expiratory wheezes
- Diagnostic testing

Case Example

A 27 year-old woman, mother of two, finds that every “cold” settles into her chest, with paroxysmal coughing, a “wheezy cough,” and cough that lingers for weeks. She reports a history of eczema as a child and mild symptoms of seasonal allergic rhinitis.
Pulmonary Function Testing

Variable expiratory airflow obstruction
- Varies over time
- Improves following bronchodilator
- Can be induced by provocative stimuli
  - e.g., methacholine

Interpreting PFTs

Significant bronchodilator response:
- Increase in FEV₁ of 12% and
- Absolute increase of 200 ml
“Asthmatic response”:
- Variably defined as 15% or 20% increase in FEV₁ following BD

Potential Bio-Markers of Airway Inflammation in Asthma

- Exhaled nitric oxide
- Sputum eosinophilia
- Exhaled breath condensate

Achieving Asthma Control

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“Inciters” of Asthmatic Inflammation

“Inciters” both trigger asthmatic symptoms and induce increased asthmatic airway inflammation:
- Cigarette smoking
- Viral respiratory tract infections
- Inhaled aeroallergens

Common Aeroallergens

- Furry animals
- Dust mites
- Mold
- Cockroaches
- Pollens

Diagnostic Testing:
- Allergy skin tests
- Blood tests (RAST)
Role of Inhaled Allergens

Allergic Sensitivity (Atopy) + Intense Allergen Exposure \[\Rightarrow\] More Severe Asthma

The Environmental Intervention

- 6 educational modules: dust mites; cigarette smoking; pets; cockroaches; rodents; and mold.
- Equipment and support:
  - Allergen-impermeable bed wraps
  - HEPA-filtered vacuum cleaners
  - HEPA room air filter
  - Cockroach extermination

Achieving Asthma Control

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Modern Therapeutic Paradigm

Controllers:
- Inhaled steroids
- Long-acting inhaled beta-agonists
- Leukotriene blockers
- Biologics (anti-IgE)

Quick-Relievers:
- Quick-acting beta-agonist bronchodilators

Step 1 (Intermittent Asthma)

- Short-acting bronchodilator as needed
- Short-acting bronchodilator prior to exercise

Short-Acting Beta-Agonists

- Albuterol
- Levalbuterol (single-isomer of albuterol)
Step 2 (Mild Persistent Asthma)

- Preferred: Low-dose inhaled corticosteroid
- Alternatives:
  - Leukotriene receptor antagonists

Inhaled Steroid Preparations

<table>
<thead>
<tr>
<th></th>
<th>mcg/puff</th>
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<tbody>
<tr>
<td>Budesonide DPI*</td>
<td>90, 180</td>
</tr>
<tr>
<td>Mometasone DPI*</td>
<td>110, 220</td>
</tr>
<tr>
<td>Beclomethasone MDI*</td>
<td>40, 80</td>
</tr>
<tr>
<td>Fluticasone MDI</td>
<td>44, 110, 220</td>
</tr>
<tr>
<td>Fluticasone DPI</td>
<td>50, 100, 250</td>
</tr>
<tr>
<td>Ciclesonide MDI*</td>
<td>80, 160</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>80</td>
</tr>
<tr>
<td>Fluticasone furoate*</td>
<td>100, 200</td>
</tr>
</tbody>
</table>

* category B in pregnancy
* approved for once-daily dosing
* small particle size

Leukotriene-Modifying Drugs

- Leukotriene receptor blockers
  - Montelukast
  - Zafirlukast
- Lipoxygenase inhibitor
  - Zileuton

Arachidonic Acid Pathway

Membrane Phospholipids

- Phospholipase A2

Arachidonic Acid

- Cyclooxygenase
- 5-lipoxygenase

Prostaglandins
- Thromboxanes

Leukotrienes
- C4, D4, E4

Cysteinyl leukotriene receptor

Leukotriene-Modifying Drugs: Clinical Effects

- Overall, less effective than ICS, but some patients respond well and compliance is higher than for inhalers.
- No good predictors of response: therapeutic trial is needed (over 3-4 weeks).
Step 3 (Moderate Persistent Asthma)

Equal weight given to two therapeutic options:

- Add LABA to low dose of ICS
- or -
- Increase the dose to ICS to medium-dose range

Adding Salmeterol vs. Increasing the Dose of Inhaled Corticosteroids

- 426 patients at 99 general practitioner centers
- Symptomatic despite BDP 400 µg/day
- Randomized to:
  - **BDP 400 µg/day plus salmeterol 50 µg BID** vs. **BDP 1000 µg/day**
- Double-blind, double-dummy 6-month trial


Salmeterol in Moderate Asthma: Peak Flow

Change in PEF (L/min)

Mean Morning PEF

Salmeterol Multicenter Asthma Research Trial (SMART)

- 26,000 subjects (of planned 60,000) randomized to salmeterol vs placebo plus "usual care" for 6 months
- Outcomes: respiratory/asthma deaths and near-deaths (respiratory failure)


Safety Concerns Regarding Long-Acting Inhaled Beta-Agonists

**WARNING:** DATA FROM A LARGE PLACEBO-CONTROLLED US STUDY THAT COMPARED THE SAFETY OF SALMETEROL (SEREVENT® INHALATION AEROSOL) OR PLACEBO ADDED TO USUAL ASTHMA THERAPY SHOWED A SMALL BUT SIGNIFICANT INCREASE IN ASTHMA-RELATED DEATHS IN PATIENTS RECEIVING SALMETEROL (13 DEATHS OUT OF 13,176 PATIENTS TREATED FOR 28 WEEKS) VERSUS THOSE ON PLACEBO (3 OF 13,179) (SEE WARNINGS AND CLINICAL TRIALS: ASTHMA: SALMETEROL MULTI-CENTER ASTHMA RESEARCH TRIAL).

Salmeterol Multicenter Asthma Research Trial (SMART)

- Findings at time of study termination:
  -- more asthma deaths (13 vs. 3) and more life-threatening or fatal asthma events (37 vs. 22) in the salmeterol-treated group.
- Subgroups at particular risk:
  -- African-Americans
  -- those not on inhaled steroids
Salmeterol Multicenter Asthma Research Trial (SMART)

“The data from SMART are not adequate to determine whether concurrent use of inhaled corticosteroids provides protection from the risk of serious outcomes.”

-- GlaxoSmithKline in collaboration with the FDA

FDA-Mandated Trials on the Safety of Inhaled LABAs

- 4 placebo-controlled RCTs of ICS + LABA vs. ICS alone in adults (N = 11,700 each) and 1 in children 4-11 years (N = 6,200)
- Primary end point: composite of hospitalization, intubation, and asthma-related deaths
- 90% power to detect doubling of relative risk
- Begun in 2011, results in 2017


Alternative Long-Acting BD: Anti-Cholinergic (Tiotropium)

- 210 subjects with asthma poorly controlled on beclomethasone 160 mcg/day
- Randomly assigned to:
  - Beclomethasone 320 mcg/day
  - Beclo 160 mcg/day + Salmeterol BID
  - Beclo 160 mcg/day + Tiotropium qD


Combination ICS and Long-Acting Bronchodilators

Combination inhalers:
- Fluticasone + salmeterol
  - MDI 45/21, 115/21, 230/21
  - DPI 100/50, 250/50, 500/50
- Budesonide + formoterol
  - MDI 80/4.5, 160/4.5
- Mometasone + formoterol
  - MDI 100/5, 200/5

“Stepping Down” Asthma Therapy

Once good asthma control is achieved, attempt to:
- stop the long-acting beta-agonist bronchodilator;
- reduce the dose of inhaled corticosteroids

Achieving Asthma Control

The Five-Point Plan:
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Key Components of an Asthma Action Plan

Teach your patients to:
• Recognize when they are having an asthma attack;
• Assess the severity of the attack;
• Have a plan to respond to the attack; and
• Know when and how to get help.

Key Components of an Asthma Action Plan

• … and put it in writing!

Traffic-Light Model: Green-Yellow-Red Zones

• Green zone: PEFR 80 – 100%
• Yellow zone: PEFR 50 – 80%
• Red zone: PEFR <50%

General Strategies

• Use your quick-relief bronchodilator more frequently than usual
• Increase your dose of inhaled steroids
• For severe attack, begin or increase dose of oral steroids

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Indications for Specialist Consultation

• Uncertainty regarding diagnosis;
• Failure to achieve good asthma control;
• Frequent need for systemic steroids;
• Frequent ED visits or hospitalizations;
• Unacceptable medication side-effects.
Evaluation of Difficult-to-Control Asthma: Systematic Approach

- Inciting agents
- Aggravating conditions
- Medication non-compliance
- Alternative diagnoses

Novel Therapies for Difficult-to-Control Asthma

- Anti-IgE monoclonal antibody (omalizumab)
- Bronchial thermoplasty

Omalizumab Characteristics

- Humanized mAb against IgE
- Binds circulating IgE regardless of specificity
- Forms small, biologically inert Omalizumab:IgE complexes
- Does not activate complement

Omalizumab: Study Outcomes

**Efficacy:**
- Fewer, shorter asthmatic exacerbations
- Reduced steroid doses
- Less need for bronchodilator
- Improved lung function and symptom scores

**Adverse effects:**
- Anaphylactic reactions (1:1000)
- Increased risk of neoplasm
- Increased incidence of cardiovascular events

Anti-IgE Monoclonal Antibody: Omalizumab (Xolair)

**Indications:** Severe, atopic asthma: total serum IgE 30 – 700 IU/ml; sensitivity to ≥1 perennial antigen.

**Benefits:** Dominant effect: fewer exacerbations

**Negatives:** Cost; small risk of anaphylaxis; injections given every 2-4 weeks indefinitely.

Bronchial Thermoplasty

**Efficacy:**
- Improved AQOL score
- Fewer asthmatic exacerbations
- Fewer ED visits
- Fewer days missed work/school

**No significant differences:**
- Morning PEF
- Symptom-free days
- Rescue medication use
- Symptom score or ACQ

Bronchial Thermoplasty

Adverse events:
- Hospitalization for respiratory symptoms (8.4%)
- Worsening asthma
- Segmental atelectasis
- Lower RTI
- Hemoptysis (treated with bronchial artery embolization)
- Aspirated tooth


Conclusion

- Good asthma control is an achievable goal in the vast majority of patients and has an impact on asthma morbidity and mortality.