Conflicts of Interest

None.
Outline

- Diagnosis
- Assessment
- Treatment
Case Example

A 6-year-old boy newly develops persistent coughing and noisy, whistling breathing every time that he goes out to play in the cold air – and has similar symptoms after sitting with the pet cat.
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.
Establishing the Correct Diagnosis

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

Variable expiratory airflow obstruction

- Varies over time
- Improves following bronchodilator
- Can be induced by provocative stimuli
  - e.g., methacholine
Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

Shawn D. Aaron, MD; Katherine L. Vandemheen, MScN; J. Mark FitzGerald, MD; Martha Ainslie, MD; Samir Gupta, MD; Catherine Lemière, MD; Stephen K. Field, MD; R. Andrew McLvor, MD; Paul Hernandez, MD; Irvin Mayers, MD; Sunita Mulipuru, MD; Gonzalo G. Alvarez, MD; Smita Pakhale, MD; Ranjeeta Mallick, PhD; Louis-Philippe Boulet, MD; for the Canadian Respiratory Research Network


- 467 adults with physician diagnosis of asthma within last 5 years.
- 33% had diagnosis of current asthma excluded by thorough evaluation.
- More than half with erroneous diagnosis of asthma had not undergone testing for airflow limitation at time of diagnosis.
Definition of Obstructive Abnormality

- Reduced FEV$_1$/FVC  \(\rightarrow\) obstructive defect
- Normal or increased FEV$_1$/FVC  \(\rightarrow\) no obstruction
Interpreting PFTs

Significant bronchodilator response:

• Increase in FEV$_1$ of 12% and
• Absolute increase of 200 ml

“Asthmatic response”:

• Variably defined as 15% or 20% increase in FEV$_1$ following BD
Bronchial Hyperresponsiveness

Low $PC_{20}$ / High BHR

High $PC_{20}$ / Low BHR

Increasing Dose of Stimulus
Potential Bio-Markers of Airway Inflammation in Asthma

- Exhaled nitric oxide
- Sputum eosinophilia
- Exhaled breath condensate

Nitrogen oxide analyzer
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.

Does she have “Reactive Airways Disease?”
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.

Does she have “Reactive Airways Disease?”
Outline

- Diagnosis
- Assessment
- Treatment
## 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><strong>Intermittent</strong></td>
<td>&lt;2 days/wk</td>
<td>&lt;2 nights/mo.</td>
<td>≥80</td>
</tr>
<tr>
<td><strong>Mild persistent</strong></td>
<td>3-6 days/wk</td>
<td>3-4 nights/mo.</td>
<td>≥80</td>
</tr>
<tr>
<td><strong>Moderate persistent</strong></td>
<td>Daily</td>
<td>&gt;5 nights/mo.</td>
<td>&gt;60 - &lt;80%</td>
</tr>
<tr>
<td><strong>Severe persistent</strong></td>
<td>Continual</td>
<td>Frequent</td>
<td>≤60%</td>
</tr>
</tbody>
</table>
Goal of Well-Controlled Asthma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Daytime Symptoms</th>
<th>Nighttime Symptoms</th>
<th>Lung Function (FEV&lt;sub&gt;1&lt;/sub&gt; or PEFR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>≤2 days/wk</td>
<td>≤2 nights/mo.</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>3-6 days/wk</td>
<td>3-4 nights/mo.</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily</td>
<td>&gt;5 nights/mo.</td>
<td>&gt;60 - &lt;80%</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>Continual</td>
<td>Frequent</td>
<td>≤60%</td>
</tr>
</tbody>
</table>
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

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. During the past **4 weeks**, how often have you had shortness of breath?

<table>
<thead>
<tr>
<th>More than once a day</th>
<th>Once a day</th>
<th>3 to 6 times a week</th>
<th>Once or twice a week</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

<table>
<thead>
<tr>
<th>4 or more nights a week</th>
<th>2 or 3 nights a week</th>
<th>Once a week</th>
<th>Once or twice</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

<table>
<thead>
<tr>
<th>3 or more times per day</th>
<th>1 or 2 times per day</th>
<th>2 or 3 times per week</th>
<th>Once a week or less</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. How would you rate your **asthma** control during the past **4 weeks**?

<table>
<thead>
<tr>
<th>Not controlled at all</th>
<th>Poorly controlled</th>
<th>Somewhat controlled</th>
<th>Well controlled</th>
<th>Completely controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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Asthma Control Test

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

- All of the time: 1
- Most of the time: 2
- Some of the time: 3
- A little of the time: 4
- None of the time: 5

2. During the past 4 weeks, how often have you had shortness of breath?

- More than once a day: 1
- Once a day: 2
- 3 to 6 times a week: 3
- Once or twice a week: 4
- Not at all: 5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

- 4 or more nights a week: 1
- 2 or 3 nights a week: 2
- Once a week: 3
- Once or twice a week: 4
- Not at all: 5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

- 3 or more times per day: 1
- 1 or 2 times per day: 2
- 2 or 3 times per week: 3
- Once a week or less: 4
- Not at all: 5

5. How would you rate your asthma control during the past 4 weeks?

- Not controlled at all: 1
- Poorly controlled: 2
- Somewhat controlled: 3
- Well controlled: 4
- Completely controlled: 5

Well-controlled asthma: >20

Copyright 2002, by QualityMetric Incorporated.
Asthma Control Test is a trademark of QualityMetric Incorporated.
In patients on regular controller medication:

- **Is asthma poorly controlled?** If yes, *step up* therapy.

- **Is asthma well controlled?** If yes, continue current treatment or *step down* therapy.
Exploring the Cause(s) of Poorly Controlled Asthma

- Inciting agents
- Aggravating conditions
- Medication non-compliance
- (Alternative diagnoses)
“Inciters” of Asthmatic Inflammation

“Inciters” both trigger asthmatic symptoms \textit{and} induce increased asthmatic airway inflammation:

- Cigarette smoking
- Air pollution
- Viral respiratory tract infections
- \textit{Inhaled aeroallergens}
Common Aeroallergens

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

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

Diagnostic Testing:

Allergy skin tests
Blood tests (RAST*)

*radioallergosorbent test (serum specific IgE test)
Role of Inhaled Allergens

Allergic Sensitivity (Atopy)

+ Intense Allergen Exposure

More Severe Asthma
Results of a Home-Based Environmental Intervention among Urban Children with Asthma

Wayne J. Morgan, M.D., C.M., Ellen F. Crain, M.D., Ph.D., Rebecca S. Gruchalla, M.D., Ph.D., George T. O’Connor, M.D., Meyer Kattan, M.D., C.M., Richard Evans III, M.D., M.P.H., James Stout, M.D., M.P.H., George Malindzak, Ph.D., Ernestine Smartt, R.N., Marshall Plaut, M.D., Michelle Walter, M.S., Benjamin Vaughn, M.S., and Herman Mitchell, Ph.D., for the Inner-City Asthma Study Group*

Mean Maximal Number of Days with Symptoms for Every Two-Week Period before a Follow-up Assessment during the Two Years of the Study

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
Outline

• Diagnosis
• Assessment
• Treatment
Goals of Modern Asthma Care

• Minimize symptoms/maximize function
• Prevent asthma attacks
• Minimize medication side-effects
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
Modern Therapeutic Paradigm

Controllers:
• Inhaled steroids
• Long-acting inhaled bronchodilators
• Leukotriene blockers
• Biologics (anti-IgE, anti-IL5)

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 metered-dose inhaler (MDI)
  - ProAir, Proventil, Ventolin
- Levoalbuterol MDI (single-isomer of albuterol)
  - Xopenex
- Albuterol dry-powder inhaler (DPI)
  - Proair Respiclick
Step 2 (Mild Persistent Asthma)

- Preferred: Low-dose inhaled corticosteroid
- Alternatives:
  - Leukotriene receptor antagonist
# Inhaled Steroid Preparations

<table>
<thead>
<tr>
<th>Steroid Preparations</th>
<th>mcg/puff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide DPI* Pulmicort</td>
<td>90, 180</td>
</tr>
<tr>
<td>Mometasone MDI-HFA* Asmanex</td>
<td>100, 200</td>
</tr>
<tr>
<td>Mometasone DPI* Asmanex Twisthaler</td>
<td>110, 220</td>
</tr>
<tr>
<td>Beclomethasone MDI-HFA* Qvar</td>
<td>40, 80</td>
</tr>
<tr>
<td>Fluticasone MDI-HFA Flovent</td>
<td>44, 110, 220</td>
</tr>
<tr>
<td>Fluticasone DPI Flovent Diskus</td>
<td>50, 100, 250</td>
</tr>
<tr>
<td>Fluticasone furoate DPI* Arnuity</td>
<td>100, 200</td>
</tr>
<tr>
<td>Ciclesonide MDI-HFA* Alvesco</td>
<td>80, 160</td>
</tr>
<tr>
<td>Flunisolide MDI-HFA Aerospan</td>
<td>80</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

Prostaglandins
Thromboxanes

5-lipoxygenase

Leukotrienes
C₄, D₄, E₄

Cysteinyl leukotriene receptor
Arachidonic Acid Pathway

Membrane Phospholipids

Phospholipase A₂

Arachidonic Acid

Cyclooxygenase

5-lipoxygenase

Prostaglandins
Thromboxanes

Leukotrienes
C₄, D₄, E₄

Aspirin
NSAIDs

Cysteinyl leukotriene receptor

C₄, D₄, E₄
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).
Role for Leukotriene Modifiers

- Effective in some patients with mild asthma
- Can be combined with inhaled steroids in more severe asthma
- Especially appropriate in aspirin-sensitive asthma
- Few side effects (mood alteration/depression)
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

Mean Morning PEF

Change in PEF (L/min)

Weeks of Treatment

Greening et al., Lancet 1994; 344:291
Safety Concerns Regarding Long-Acting Inhaled Beta-Agonists

Black Box warning regarding salmeterol:

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)

- 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)

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
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

Fluticasone + Salmeterol vs. Fluticasone alone

- Among 11,679 patients randomized to fluticasone (in 3 doses) vs. fluticasone (3 doses) plus salmeterol
- No deaths; only 2 intubations (both in fluticasone alone group); overall no difference in “serious adverse events”
- Fewer severe asthma exacerbations in group treated with fluticasone + salmeterol.

Figure 4-5. Stepwise Approach for Managing Asthma in Youths ≥12 Years of Age and Adults

Intermittent Asthma

Persistent Asthma: Daily Medication
- Consult with asthma specialist if step 4 care or higher is required.
- Consider consultation at step 3.

Step 1
Preferred: SABA PRN

Step 2
Preferred: Low-dose ICS
Alternative: Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3
Preferred: Medium-dose ICS + LABA
Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4
Preferred: High-dose ICS + LABA + oral corticosteroid
Consider Omalizumab for patients who have allergies

Step 5
Preferred: High-dose ICS + LABA + oral corticosteroid
Consider Omalizumab for patients who have allergies

Step 6
Preferred: High-dose ICS + LABA + oral corticosteroid + environmental control
Consider Omalizumab for patients who have allergies

Each step: Patient education, environmental control, and management of comorbidities.
Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

Step up if needed (first, check adherence, environmental control, and comorbid conditions)
Assess control
Step down if possible (and asthma is well controlled at least 3 months)

## Combination ICS and LABA

<table>
<thead>
<tr>
<th>Combination</th>
<th>Brand name</th>
<th>Dose per inhalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone + salmeterol</td>
<td>Advair Diskus</td>
<td>100/50, 250/50, 500/50</td>
</tr>
<tr>
<td></td>
<td>Advair HFA</td>
<td>44/21, 115/21, 230/21</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>Symbicort HFA</td>
<td>80/4.5, 160/4.5</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>Dulera HFA</td>
<td>100/5, 200/5</td>
</tr>
<tr>
<td>Fluticasone furoate + Vilanterol*</td>
<td>Breo DPI</td>
<td>100/25, 200/25</td>
</tr>
</tbody>
</table>

*Once-daily dosing*
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

Adding tiotropium to ICS was non-inferior to adding salmeterol in all outcomes measured.

“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

to minimize the potential risk for severe asthmatic attacks and long-term side effects.
Novel Asthma Therapies

- Anti-IgE monoclonal antibody, omalizumab *Xolair*
- Anti-IL-5 monoclonal antibodies, mepolizumab *Nucala* and reslizumab *Cinqair*
- Bronchial thermoplasty
Asthma Action Plan: 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
Traffic-Light Model: Green-Yellow-Red Zones

- **Green zone**: PEFR 80 – 100%
- **Yellow zone**: PEFR 50 – 80%
- **Red zone**: PEFR <50%
Managing Asthmatic Attacks

- Oral corticosteroids (prednisone 40-60 mg/day)
  - oral = i.v.
  - no taper necessary
  - duration? – until lung function close to baseline
  - start or continue inhaled steroids thereafter
Trends in Asthma Deaths in U.S.

Asthma Mortality in the United States

Age-Adjusted Death Rates per 100,000 Persons


0 0.5 1 1.5 2 2.5

Epidemiology of Asthmatic Attacks

- 3,400 deaths/year
- 439,000 hospitalizations/year
- 2.1 million ED visits/year

Asthma Fact Sheet, 2012
American Lung Association (data for 2009)
Summary

- A diagnosis of asthma is suspected based on history and possibly physical exam and is confirmed by documentation of variable airflow obstruction on spirometry.

- In patients on therapy for asthma, assess asthma control – based on symptoms, lung function, and frequency of exacerbations.
Summary (cont).

- In patients with poorly controlled asthma, consider: **inciting agents** (esp. allergens), **aggravating factors**, and **medication non-adherence**.

- **Environmental modification**, including reducing allergen exposures, can improve asthma control.
Summary (cont.)

• Regular controller therapy reduces symptoms and decreases exacerbations in patients with persistent symptoms.

• Regularly assess asthma control: step up therapy in poorly controlled asthma; maintain or step down therapy in well-controlled asthma.
Summary (cont.)

- **Novel therapies** exist for severe asthma, targeting elevated IgE, persistent eosinophilia, or smooth muscle hypertrophy.
- Help prepare patients for asthmatic exacerbations by discussing with them an “asthma action plan.”