Preventing Asthma Exacerbations

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Faculty Disclosure

• I have no financial interests/arrangements that would be considered a conflict of interest.
Course Learning Objectives

• To address the question: What defines an asthma exacerbation versus loss of asthma control?

• To discuss which patients may be at increased risk for exacerbations.

• To review why reducing exacerbation frequency may be important in terms of long term consequences.
What Is An Asthma Exacerbation?

• No consistently accepted definitions for asthma control, severity, or exacerbations.

• In clinical practice, exacerbations are identified as events characterized by:
  – a change from the patient’s previous status
  – outside the patient’s own usual range of day-to-day variation.

Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice


This Joint Statement of the American Thoracic Society and European Respiratory Society was approved by the ATS Board of Directors on March 13, 2009 and by the ERS Executive Committee on November 27, 2008.

Asthma Exacerbations

• Exacerbations are recognized as a common clinical manifestation in patients with severe asthma, and are known to increase the risk of asthma mortality.

• However, even in patients thought to have mild asthma, the rates of severe asthma exacerbations have been much higher than expected.
Asthma Exacerbations

- Exacerbations vary considerably in:
  - Speed of onset, from minutes or hours to 2 weeks
  - Time to resolution (5 to 14+ days)
  - Absolute severity, both between and within individual patients.
Asthma Exacerbations

• For individual patients, information about the onset and course of exacerbations should subsequently be used to refine and customize the “trigger points” or “action points” for the patient’s asthma action plan.
Asthma Exacerbations and Children

- In young children, exacerbations are frequent, with significant morbidity, possibly because of frequency of viral infections.

- No reliable methods for early detection, but the development of upper airway symptoms of viral infection may be a useful alert.

- Severity of exacerbations is difficult to characterize in children because of dependence on parental reporting and difficulty of measuring lung function.

- Many exacerbations in children are treated with increased doses of ICS (moderate) rather than systemic corticosteroids (severe).
Asthma Exacerbations

• Prevention of asthma exacerbations has been identified in all asthma treatment guidelines as an important component of establishing ideal asthma control.

• Exacerbations are the most important outcome because:
  – they constitute the greatest risk to patients,
  – are a cause of anxiety to patients and their families
  – result in the greatest stress on health care providers
  – generate the greatest cost to the health care system

• Only in the past 10 years have exacerbations been used as a primary outcome variable in clinical trials.
Classification Of Exacerbations

- Severe
- Moderate
- Mild
What Is A Severe Asthma Exacerbation?

• Events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma.

• Should include at least 3 days use of systemic corticosteroids.

• Marker of poor asthma control.
What Is A Moderate Asthma Exacerbation?

• Events that are troublesome to the patient, and that prompt a need for a change in treatment, but are not severe.

• Deterioration in symptoms and/or lung function with increased rescue bronchodilator use that lasts >2 days, but is not severe enough to warrant systemic corticosteroids and/or a hospital visit.

• These events are clinically identified by being outside the patient’s usual range of day-to-day asthma variation.
What Is A Mild Asthma Exacerbation?

• Although several studies have reported “mild” exacerbations, these episodes are typically only just outside the normal range of variation for the individual patient.

• With present methods of analysis, they could not be distinguished from transient loss of asthma control.

• Hence, no definition of a “mild” exacerbation can be offered.
What is Asthma Control?

• The extent to which the various manifestations of asthma have been reduced or removed by treatment. This includes two components:

  1. Level of clinical asthma control, which is gauged from features such as symptoms and the extent to which the patient can carry out activities of daily living and achieve optimum quality of life.

  2. Risk of future adverse events including loss of control, exacerbations, accelerated decline in lung function, and side-effects of treatment.
Asthma Is Not A Static Disease: Clinical Control Can Be Difficult to Define

- Good control
- Poor control

- Wheezing
- Dyspnea
- Cough
- Use of rescue medication
- FEV$_1$
- PEF variability
## Classifying Asthma Control Impairment

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td>≤2 d/wk</td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 d/wk but not more than once a day</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td>1x/mo</td>
</tr>
<tr>
<td></td>
<td>≤1x/mo</td>
</tr>
<tr>
<td></td>
<td>≤2x/mo</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Short-acting $\beta_2$-agonist use for symptom control (not prevention of EIB)</td>
<td>≤2 d/wk</td>
</tr>
<tr>
<td>Lung function:</td>
<td>&gt;80% of predicted/ personal best</td>
</tr>
<tr>
<td>• FEV₁ or peak flow</td>
<td>&gt;80% of predicted/ personal best</td>
</tr>
<tr>
<td>• FEV₁/FVC</td>
<td>&gt;80% of predicted</td>
</tr>
<tr>
<td>Validated questionnaires</td>
<td>ATAQ 0 ≤0.75* ≤20</td>
</tr>
<tr>
<td>ACQ</td>
<td>1–2 16–19</td>
</tr>
<tr>
<td>ACT</td>
<td>1–2 16–19</td>
</tr>
</tbody>
</table>

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.
# Classifying Asthma Control

## Risk

<table>
<thead>
<tr>
<th>Components of Control</th>
<th>Classification of Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0–1/year</td>
</tr>
<tr>
<td>Possible treatment-related adverse effects</td>
<td>Possible 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>
<tr>
<td>Reduction in lung growth</td>
<td>Evaluation requires long-term follow-up care.</td>
</tr>
<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term follow-up care.</td>
</tr>
</tbody>
</table>

Uncontrolled Asthma

– Any one of the following:
  • *Poor symptom control:* ACQ consistently >1.5 (or “not well controlled” by NAEPP guidelines)
  • *Frequent exacerbations:* 2 or more bursts of systemic CSs (>3 days each) in previous year
  • *Severe exacerbations:* at least 1 hospitalization, ICU stay or mechanical ventilation in previous yr
  • *Persistent airflow limitation:* pre-short and long acting bronchodilator FEV1 < 80% predicted (in the face of reduced FEV1/FVC)
Time-course Of Improvement In Different Asthma Control Outcome Variables With ICS

Redell et al, ERJ, 2000
### What Is Asthma Severity?

#### Traditionally Defined Off Treatment

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Youths ≥12 years of age and adults)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermittent</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
</tr>
<tr>
<td>Normal FEV₁/FVC</td>
<td></td>
</tr>
<tr>
<td>8–19 yr</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>20–39 yr</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>40–59 yr</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>60–80 yr</td>
<td>≤2 days/week</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>
<tr>
<td>Risk</td>
<td>Exacerbations requiring oral systemic corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category.</td>
</tr>
</tbody>
</table>

Relative annual risk of exacerbations may be related to FEV₁

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What Is Asthma Severity?

A new perspective on concepts of asthma severity and control

What Is Asthma Severity?

• The difficulty in controlling asthma with treatment after exclusion of modifiable factors such as:
  – Poor adherence
  – Smoking
  – Comorbidities

• Severity largely reflects the required level of treatment and the activity of the underlying disease state during treatment, which may vary depending on the underlying phenotype, environmental factors, and comorbidities.

• There is clinical utility in distinguishing patients with “difficult-to-treat” or severe asthma from those who have “easy-to-treat” or mild asthma.
New Asthma Severity Definition

• Represents a change from previously published definitions as represented by clinical features before commencement of treatment.

• Insufficient research evidence that a patient’s clinical characteristics when untreated could:
  – Inform future management decisions
  – Predict the ease or difficulty of obtaining good asthma control once treatment was commenced
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Common usage of the terms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“Severity”</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>The intensity of respiratory distress when asthma symptoms/episodes/attacks occur</td>
</tr>
<tr>
<td><strong>Exacerbations</strong></td>
<td>The speed of onset (rapidity), degree of disability, and advent of respiratory failure</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>Amount of treatment required to maintain best symptom control and lung function</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>The degree of loss of lung function</td>
</tr>
<tr>
<td><strong>Airway hyperresponsiveness</strong></td>
<td>The level of response to challenge agents e.g. methacholine, exercise</td>
</tr>
<tr>
<td><strong>Airway inflammation</strong></td>
<td>The degree of inflammation present when untreated</td>
</tr>
</tbody>
</table>
Severe Asthma Defined As The Requirement For (Not Just The Prescription Or Use Of) High-intensity Treatment, After Modifiable Factors And Comorbidities Have Been Appropriately Managed

Severe asthma
(i.e. requiring high-intensity treatment)

Good control only if on high-intensity treatment

Poor control despite high-intensity treatment

Potentially treatment responsive, but with persistent problems, e.g. poor compliance, persisting allergen exposure, smoking etc.

Persistent comorbidities, e.g. psychosocial problems or reflux, despite treatment

Treatment resistant (sometimes called refractory asthma)
Relationship Between Asthma Phenotype, Severity And Control
Severity, Control, and Responsiveness Are Related

Select Appropriate Therapy Step
Step therapy up or down
1. Symptoms and lung function represent different domains of asthma:
   - correlate poorly over time in individual patients
   - both need to be monitored in clinical practice

2. Long-term diaries are not needed for clinical management of asthma in majority of patients:
   - may be relevant in “poor perceivers”
   - patients with frequent exacerbations.
3. When patients are carrying out ambulatory lung function monitoring, their monitoring device should also be used for testing in office, to allow appropriate comparison.

4. Lung function diary monitoring upper limit of normal for amplitude % mean with twice-daily monitoring is 8%, not traditionally quoted cut-point of 15 to 20%.