Defining and diagnosing severe asthma

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Presenter Disclosures

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Lecture Fees: AstraZeneca, Alk Abello, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Nycomed, Pfizer, TEVA

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Defining and diagnosing severe asthma

Learning objectives

- To review new definitions of severe asthma
  - WHO
  - ATS/ERS Task Force on Severity and Control
  - ATS/ERS Task Force on Severe Asthma

- Consider the clinical implications of these definitions
Asthma is not a single disease!

Asthma phenotypes

“The characteristics of an organism which develop as a consequence of interactions of the genetic background with the environment...”

ATN/ERS Task Force on Severe Asthma 2009: Co-Chairs: Sally Wenzel & Fan Chung
Conceptual framework asthma and its management (ATS/ERS Task Force)

ASTHMA CONTROL
Current control → Future risk

ASTHMA SEVERITY
("difficulty in treating")

DISEASE ACTIVITY

ASTHMA PHENOTYPES

TREATMENT

Genetic and environmental factors

Taylor DR et al, ERJ 2008; 32:545-554
## Severity Classification: Cockcroft

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
<th>Level of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very mild</td>
<td>None or rare β2-agonist</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Mild</td>
<td>Rare β2-agonist, low-dose ICS</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate to high-dose ICS + occasional OCS</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Severe</td>
<td>High- to very high-dose ICS + occasional OCS</td>
<td>Well controlled</td>
</tr>
<tr>
<td>Very severe</td>
<td>Very high dose ICS + Oral CS + additional therapies</td>
<td>Not well controlled</td>
</tr>
</tbody>
</table>


Stoloff SW, Boushey HA. JACI 2006
SARP: Assessment of Asthma Phenotypes

628 variables from 726 patients

353 questionnaire data

Demographics
1 Sex
2 Race
3 BMI
4 Age
5 Onset of asthma
6 Asthma duration

COMPOSITE VARIABLES:
14-17 medication use
18-19 Health care utilization
20-21 Symptoms
26-29 Asthma triggers
30 Co-morbidities
31-32 Family history
33 Tobacco exposure
34 Women/hormones

197 Lung function

Lung function
7-9 pre b.d. afo
10-12 post b.d. response to albuterol
PC20 Meth

19 Atopy

13 Skin tests
Composite variables
22, 23 - Perennial allergens
24, 25 - Seasonal allergens

59 Biomarkers

IgE
FeNO
Sputum
BAL

34 variables in cluster analysis

11 variables in discriminant analysis

3 variables in tree analysis

Moore, WC et al, AJRCCM 2009: epub
Severe Asthma Research Program (SARP)
Severe Asthma Research Programme: Phenotyping by Cluster Analysis

628 variables
34 core variables
726 patients

Cluster 1
Cluster 2
Cluster 3
Cluster 4
Cluster 5

Branch based on treatment responsiveness

Moore, WC et al, AJRCCM 2009: epub
Severe Asthma Research Program (SARP)
Using only pre- and post-bronchodilator FEV1% predicted and age of onset, 80% were correctly assigned.

% = percentage of patients from that cluster correctly assigned

N = 728

Moore, WC et al, AJRCCM 2009: epub
Severe Asthma Research Program (SARP)
Severe asthma requiring high intensity treatment

ATS / ERS Task Force Asthma Control and Exacerbations
Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice

“Severe asthma is defined as the requirement for high intensity treatment after modifiable factors and comorbidities have been appropriately managed”

Good control on high intensity treatment

Poor control despite high intensity treatment

- Treatment responsive, but with persistent problems e.g. poor adherence, smoking
- Persistent co-morbidities e.g. GE reflux, obesity
- Treatment resistant/refractory asthma

• All severe asthma requires confirmed diagnosis of asthma, compliance/adherence and co-morbidities addressed.

• All severe asthma requires treatment with “gold standard medication” (for that age group) for 3 months by asthma specialist* to prevent patient from becoming uncontrolled or which remains uncontrolled.

• *Asthma specialist can vary from country to country and from children to adults. In adults, this is traditionally an allergist or pulmonologist/respirologist with advanced training and experience in asthma. In pediatric populations this may also include pediatricians with additional training and experience in severe asthma.

Bousquet J et al, JACI 2010
Definition of Severe or Difficult to Manage Asthma:

Gold Standard Therapy

High dose inhaled CS and LABA (or LT modifier) and / or systemic CS for ≥50% of the previous year.

High dose ICS is fluticasone ≥1000 mcg/day (or equivalent)
<table>
<thead>
<tr>
<th>CONTROL OPTIONS</th>
<th>SELECT ONE</th>
<th>SELECT ONE</th>
<th>ADD ONE OR MORE</th>
<th>ADD ONE OR BOTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>low-dose ICS*</td>
<td>low-dose ICS plus</td>
<td>medium- or high-dose</td>
<td>glucocorticosteroids</td>
<td></td>
</tr>
<tr>
<td>leukotriene modifier**</td>
<td>long-acting β₂-agonist</td>
<td>ICS plus long-acting</td>
<td>treatment</td>
<td></td>
</tr>
<tr>
<td>low-dose ICS plus leukotriene modifier</td>
<td>sustained-release theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low-dose ICS plus sustained-release theophylline</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*Inhaled glucocorticosteroids
**Receptor antagonist or synthesis inhibitors

Failed Step 3
Levels of CONTROL achieved in GOAL
Total or Well Controlled* at 52 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of patients CONTROLLED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salm/FP 500 Fluticasone 500</td>
<td>n = 1155</td>
</tr>
<tr>
<td>Salm/FP 250 Fluticasone 250</td>
<td>62%</td>
</tr>
<tr>
<td>Salm/FP 100 Fluticasone 100</td>
<td>50%</td>
</tr>
</tbody>
</table>

*GOAL definitions of control

Patients (% per week) achieving GINA Controlled or Partly Controlled weeks during Bud/Form M&R studies

Bud/Form M&R vs High-dose ICS + SABA\textsuperscript{1,2}

Bud/Form M&R vs Same-dose ICS/LABA + SABA\textsuperscript{1,3}

Bud/Form M&R vs High-dose ICS/LABA + SABA\textsuperscript{4,5}

Bateman ED et al, JACI 2010

Definition of Severe or Difficult to Manage Asthma

Definition of 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 the previous year

• **Severe exacerbations:** at least one hospitalization, ICU stay or mechanical ventilation in the previous year

• **Persistent airflow limitation:** pre-short and long acting bronchodilator FEV1 < 80% predicted (in the face of reduced FEV1/FVC)

Bousquet J et al, JACI 2010
Future risk of exacerbations... in relation FEV₁ (pre-bronchodilator)

Kitch BT et al, Chest 2004;126:1875-82.
Definition of Severe or Difficult to Manage Asthma

- Controlled asthma on these high doses of inhaled corticosteroids or systemic CS (or additional biologics) places a patient at high future risk for side effects from medications

Bousquet J et al, JACI 2010
Exacerbation rate in maintenance phase
(according to control status achieved in phase I)

Mean exacerbation rate per patient per year

Stratum 1: ICS-naive

Stratum 3: Moderate ICS

*Requiring either oral steroids or hospitalisation / emergency visit

Patients (% per week) experiencing exacerbations requiring medical intervention

- **High-dose ICS + SABA vs Bud/Form M&R**
- **Same-dose ICS/LABA + SABA vs Bud/Form M&R**
- **Higher-dose ICS/LABA + SABA vs Bud/Form M&R**

Exacerbations in week (%)

- **Week 27**: 2.0%
- **Week 28**: 3.2%
- **Week 44**: 3.6%
- **Week 48**: 3.2%

Increasing the dose of ICS in the combination inhaler

*Bateman ED et al, JACI 2010*
Severe and difficult to manage asthma

Disease factors:
- Wrong diagnosis: Functional upper airway problems, heart disease
- Unrecognised trigger factors: drugs, occupational agents
- Associated disease: GORD, sinusitis, thyrotoxicosis
- Corticosteroid refractoriness or resistance

Health system factors:
- Inadequate or inappropriate treatment
- Failed patient / physician partnership

Patient factors:
- Poor adherence
- Psychological / personality
- Socio-behavioural
Corticosteroid refractoriness is not absolute.

- Improved asthma control
- Reduced airway inflammation (%)
- Dose of corticosteroid

- ‘normal’
- Mild asthma, steroid-responsive
- Severe asthma, ‘steroid-dependent’
- Steroid resistant

Dose of corticosteroid vs. improved asthma control and reduced airway inflammation (%).
Severe and difficult to manage asthma

*Disease factors:*
- Wrong diagnosis: Functional upper airway problems, heart disease
- Unrecognised trigger factors: drugs, occupational agents
- Associated disease: GORD, sinusitis, thyrotoxicosis
- Corticosteroid refractoriness or resistance

*Health system factors:*
- Inadequate or inappropriate treatment
- Failed patient / physician partnership

*Patient factors:*
- Poor adherence
- Psychological / personality
- Socio-behavioural / economic considerations
Patients are not all the same!

Revised NEO Personality Inventory
Costa PT & McCrae RR, 1992
Asthma Management and Prevention Programme
Component 1: Develop a doctor / patient partnership

Doctor-directed patient self-management

Written self-management plans are associated with improved asthma outcomes
Alexithymia

= difficulty in perceiving and expressing emotions and body sensations

- Prevalence: 8 - 19% of males in general population
- Toronto Alexithymia Score
- Correlates with neuroticism
- Negative correlation with Extraversion and Openness

Alexithymia more common in patients with near-fatal asthma episodes (36 versus 13%)
More severe asthma, and very severe near-fatal episodes

Serrano J et al, ERJ 2006; 28: 296

Luminet O et al, J Pers Assess 1999; 73:345
Plaza V et al, J Asthma 2006; 43: 639
Severe and Difficult to Manage Asthma

*Take home messages*

- Severe asthma is common!
- Definition is clinical
- Consider domains to establish cause
- In real life practice, patient factors are most common
- Resistance to treatment is relative and seldom complete
- New second/third line (targeted) controllers are needed