Control and prevention of asthma exacerbations

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Synopsis

- Definition of asthma control
- Main causes of asthma exacerbations
- Physiopathology & treatment targets
- How to prevent/manage exacerbations

Levels of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (All of the following)</th>
<th>Partly controlled (any present in any week)</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td></td>
</tr>
<tr>
<td>Limitations of activities</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Nocturnal symptoms / awakening</td>
<td>None</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td>Need for rescue / &quot;Reliever&quot; treatment</td>
<td>None (2 or less / week)</td>
<td>More than twice / week</td>
<td></td>
</tr>
<tr>
<td>Lung function (PEF or FEV1)</td>
<td>Normal</td>
<td>&lt; 80% predicted or personal best (if known) on any day</td>
<td></td>
</tr>
<tr>
<td>Exacerbation</td>
<td>None</td>
<td>One or more / year 1 in any week</td>
<td></td>
</tr>
</tbody>
</table>

Goal of Asthma Management

- Overall Asthma Control
  - Achieving: Current control
  - Reducing: Future risk

Exacerbations and poor control

1. Exacerbations reflect poor control and severe asthma
   - Strong association between exacerbations and poor control (Vollmer 2002)
   - Exacerbations occur despite continuing ICS in patients with difficult-to-control asthma (H T Veen, 1999)
   - Exacerbations are reduced when asthma control improves with ICS (Pauwels 1997, O’Byrne 2001, Baten 2004)
   - Prevention: change usual Rx or dose, adherence, environment

2. Exacerbations may occur despite good control of asthma
   - Viral infections, C. pneumoniae, M. pneumoniae, ± allergen, ± pollution
   - Management: different from management of poor control

Adapted from H Reddel
Asthma exacerbations: some commonly reported causes

**Viral infections**
- Rhinovirus (RV)
- Respiratory syncytial virus (RSV)
- Human metapneumovirus (HMV)
- Influenza virus

**Fungi**

**Bacteria**
- Mycoplasma pneumoniae
- Chlamydia pneumoniae
- **Indoor & outdoors allergens**
  - Indoor: domestic mites, furred animals (dogs, cats, mice), cockroach allergen, fungi, moulds, yeasts.
  - Outdoor: pollen, fungi, moulds, yeasts.

**Occupational exposures**
- Irritants - Airway pollutants - Tobacco smoke (Passive/active smoking)

Triggers & Inducers of asthma

Risk factors for exacerbations and hospital admissions in asthma of early childhood  Wever-Hess J 2000

In young children:
- Predisposing risk factors for exacerbation were:
  - damp housing (odds ratio (OR) 7.6 (2.0–28.6)
  - colds (OR 3.6 (1.4–9.6))

For recurrent exacerbations:
- sensitization to inhalant allergens (Phadiatop®) (OR 8.1 (1.6–46.1))
- damp housing (OR 3.8 (1.1–12.8))

For older children, predisposing risk factors for exacerbation were mean age at initial presentation (OR 0.92 (0.88–0.97)) and level of total IgE (OR 2.3 (1.4–3.9)), whereas for recurrent exacerbations no predictor variables were found.

Asthma at the workplace

A work in Hyde Park... or on Oxford Street  McCreanor et al. NEMJ 2007

Does air pollution increase the effect of aeroallergens on hospitalization for asthma?

- Aeroallergens are risk factors for asthma severe enough to precipitate hospitalization
- The presence of air pollution appears to increase the morbidity from aeroallergens
- Decreasing air pollution levels might reduce the severity of allergic asthma exacerbations in the general population

Calmas et al. JACI 2011
**Smoking and asthma: clinical consequences**

- Increased asthma morbidity and severity
- Reduced asthma control
- Increased health care use
- Increased rate of decline in pulmonary function
- Reduced response of asthma medications


Siroux V, et al. Relationships of active smoking to asthma and asthma severity in the EGEA study. Eur Respir J 2000


**Triggers of asthma exacerbations**

Singh B & Busse 2006

**Environmental exposures & asthma exacerbations**

Wark & Gibson Thorax 2006

**Asthma inflammatory responses/phenotypes**

NS: 117 patients

Jarayam et al. ERJ 2006

**LOMA study - Asthma Exacerbations, n = 102**

<table>
<thead>
<tr>
<th>Type of exacerbation, %</th>
<th>Eosin</th>
<th>NonE/NonN</th>
<th>Neu</th>
<th>Eos + Neu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eos</td>
<td>29.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-eos/NonN</td>
<td></td>
<td>49.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neu</td>
<td></td>
<td></td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Eos + neu</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
</tbody>
</table>
ALLERGEN-INDUCED AIRWAY INFLAMMATION

Decline in FEV1 in patients with infrequent or frequent asthma exacerbations

How to prevent asthma exacerbations?

1) Preventative measures and patient education
2) Ensure adequate baseline treatment of asthma
3) « Fine-tuning » of asthma control?
4) Regular follow-up

Environmental measures

- Tobacco smoke: Stop smoking (cessation programs). Avoidance of exposure
- Drugs, foods, and additives: Avoid if they are known to cause symptoms
- Animals with fur:
  - Use air filters.
  - Remove animals from the home/ reduce exposure
- House dust mites:
  - Wash bed linens and blankets weekly in hot water and dry (hot dryer or sun)
  - Encase pillows and mattresses in air-tight covers.
  - Replace carpets with hard flooring, especially in sleeping rooms
- Cockroaches: Clean the home thoroughly and often. Use pesticide spray but make sure the patient is not at home when spraying occurs
- Outdoor pollens and mold: Close windows and doors and remain indoors when pollen and mold counts are highest
- Indoor mold: Reduce dampness in the home; clean any damp areas frequently

Patterns of adherence to inhaled ICS - Use vs Prescribed

Asthma education is essential

Urgent visits for asthma

- Basic notions
- Inhaler technique
- Action plan
- Reference to an asthma educator

Côté et al. AJRCCM 2001

Lacasse et al. CJR 2005

Côté et al. Eur Respir J 1992
Outcomes of asthma self-management

<table>
<thead>
<tr>
<th>Overall effect</th>
<th>Effects of optimal self-management intervention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>0.64 (0.53 to 0.80)</td>
<td>0.58 (0.43 to 0.77)</td>
</tr>
<tr>
<td>Emergency visit</td>
<td>0.83 (0.73 to 0.94)</td>
<td>0.78 (0.67 to 0.91)</td>
</tr>
<tr>
<td>Unscheduled doctor visit</td>
<td>0.68 (0.56 to 0.81)</td>
<td>0.73 (0.58 to 0.92)</td>
</tr>
<tr>
<td>Days off work</td>
<td>0.72 (0.60 to 0.83)</td>
<td>0.65 (0.50 to 0.81)</td>
</tr>
</tbody>
</table>

Results are shown as relative risk (95% CI). All p < 0.05.
NNT, number needed to treat.


Action plans and asthma

<table>
<thead>
<tr>
<th>Action plan component</th>
<th>RR (95% CI)</th>
<th>Test (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% predicted PEF</td>
<td>0.44 (0.34, 0.56)</td>
<td>0.44 (0.34, 0.56)</td>
</tr>
<tr>
<td>Personal best PEF</td>
<td>0.44 (0.34, 0.56)</td>
<td>0.44 (0.34, 0.56)</td>
</tr>
<tr>
<td>4 action points</td>
<td>0.60 (0.48, 0.76)</td>
<td>0.60 (0.48, 0.76)</td>
</tr>
<tr>
<td>&lt;4 action points</td>
<td>0.29 (0.17, 0.47)</td>
<td>0.29 (0.17, 0.47)</td>
</tr>
<tr>
<td>ICS and OCS</td>
<td>0.69 (0.44, 0.90)</td>
<td>0.69 (0.44, 0.90)</td>
</tr>
</tbody>
</table>

Figure 1: Comparison of the effects of action plan components on hospital admissions for severe, ICS, inhaled corticosteroids, OCS, and controller.

Fitzgerald and Gibson Thorax 2006

Prevention of asthma exacerbations: the role of inhaled corticosteroids

Pauwels et al., Lancet 2003
- 7241 patients randomised to receive budesonide 400 mg or 200 mg vs placebo
- 198 severe exacerbations in the placebo arm
- 117 in the active treatment arm (risk ratio = 0.80, 95% CI: 0.66 to 0.97, p = 0.005)

Sin et al., JAMA 2004
- Overall relative risk (RR) of 0.46 (95% CI: 0.34 to 0.62), p < 0.001, in subjects treated with ICS compared with placebo

- Once controlled is achieved, ICS can be tapered down

ICS vs LTRAs on asthma exacerbations


The GOAL Study

Bateman et al., AJRCCM 2004

Open-label phase
For patients not achieving TOTAL CONTROL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Phase 1</td>
<td>3-week course assessment</td>
</tr>
<tr>
<td>Phase 2</td>
<td>6-week course assessment</td>
</tr>
</tbody>
</table>

STAY: Severe Exacerbations

>80% identified post-hoc

O’Byrne PM et al., Am J Respir Crit Care Med 2005; 171:129-12
Achieving good control of asthma

Bateman et al. AJRCCM 2004

WELL CONTROLLED asthma
Effect of adding oral corticosteroids

Reductions in Exacerbations with Omalizumab in High-risk Asthma


0.65
0.69
1.1
1.56

All patients
High-risk patients

Mean annualized asthma exacerbation rate

Omalizumab
Control

p<0.001
p=0.007
↓56%

Mepolizumab in severe eosinophilic asthma

Nair et al. NEJM 2009

Evaluation of asthma control with induced sputum eosinophilia


Does a strategy that minimized airway eosinophilia reduces asthma exacerbations compared to a standard management strategy?

-74 patients with moderate to severe asthma

-BTS Guidelines vs eosinophils control

-Assessment over a 12 months period

<table>
<thead>
<tr>
<th></th>
<th>Severe exacerbations</th>
<th>Hospital admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTS</td>
<td>109</td>
<td>6</td>
</tr>
<tr>
<td>Sputum eosinophils</td>
<td>35</td>
<td>1</td>
</tr>
</tbody>
</table>

(p= 0.01)  
(p= 0.047)

Type of Exacerbations per strategy, n = 102

Facebook asthma

- The sight of her ex-girlfriend profile on Facebook induced dyspnoea repeatedly in an 18 years old man
- After internet login “post-Facebook” PEF values were reduced by more than 20%
- In collaboration with a psychiatrist, the patient decided not to login to Facebook any longer and the asthma attacks stopped

D'Amato. The Lancet 2010
## Conclusions

- Asthma exacerbations are a frequent indicator of insufficient asthma control and lead to increase health care use and accelerated decline in lung function.
- Viral infections and allergen exposure are the most common causes of asthma exacerbations.
- Asthma exacerbations can be prevented by asthma education, preventative measures and adequate treatment.
- Frequent exacerbations require a reassessment of the main causes of uncontrol.