Non-viral triggers of asthma exacerbations

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Learning objectives

- Review the factors that trigger asthma exacerbations in addition to viruses
- Present data on the importance of various non-viral triggering factors of asthma exacerbations in disease management (prevention and treatment)
- Consider if various triggering mechanisms induce different pathophysiologic changes
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, molds, yeasts
- **Outdoor**: pollens, fungi, molds, yeasts

**Occupational exposures**

**Irritants - Airway pollutants - Tobacco smoke** (Passive/active smoking)
Triggers & inducers of asthma

Inflammation

- Respiratory infections
- Allergens
- Work place

Others

- Medications
- Tobacco
- Food additives
- Reflux
- Air pollution

Constriction

- Change in temperature
- Exercise
- Strong odours
- Cold air
- Emotion and stress
Mechanisms of asthma exacerbations

Singh & Busse 2006
Decline in FEV1 in patients with infrequent or frequent asthma exacerbations

Asthma inflammatory responses/phenotypes

**EOSINOPHILIC**
- May-Giemsa staining

**NEUTROPHILIC**
- Neutrophil elastase stain

**PAUCYGRANOCYTOPENIC**
- Haematoxylin and eosin stain

### Allergens
- Sensitizing agents
- Steroid reduction
- Others

### Viral & bacterial infections
- Cigarette Smoking
- Pollutants
- Occupational agents
- Exercise
- Obesity
- Others

### CS-resistant asthma
- High-doses of CS
- Others
# Causes of bronchitis in asthma

<table>
<thead>
<tr>
<th></th>
<th>Neutrophilic</th>
<th>Eosinophilic</th>
<th>Mixed neutrophilic and eosinophilic</th>
<th>Paucigranulocytic (neither)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infections</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bacterial infections</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Occupational exposures</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pollutants</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Chemical sensitisers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Allergen</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Corticosteroid reduction</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Age</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Gibson et al. Lancet 2010
LOMA study - Asthma Exacerbations

N: 117 patients

Type of exacerbation, %

- Eosin: 29.5%
- NonE/NonN: 49.0%
- Neut: 21.6%
- Eos + Neu: 4.0%

Total: 100%
Type of Exacerbations per strategy, n = 102

**Clinical Strategy**

- Eosinophilic: 38.7%
- Non eos/non neu: 43.3%
- Neutrophilic: 21.0%

**Sputum Strategy**

- Eosinophilic: 15.0%
- Non eos/non neu: 62.5%
- Neutrophilic: 22.0%

P-values:
- Eosinophilic: P = 0.008
- Non eos/non neu: P = 0.009
- Neutrophilic: P = 0.2
The number of bacteria in the human body is higher than the number of cells.
Atypical bacteria

- Atypical bacteria inconsistently associated with AAE
  - suboptimal detection?
  - significant temporal variability?
  - causality relationship?
Mycoplasma pneumoniae

- **Singh & Busse Thorax 2006:**
  - a cause of acute respiratory infections in both children and adults
  - may exacerbate underlying asthma
  - some patients with asthma may develop a chronic infection with *M pneumoniae* which, in turn, could contribute to the persistence and severity of asthma

- **Biscardi et al Clin Infect Dis 2004:**
  - 20% of patients hospitalised for severe asthma also had a documented Mycoplasma infection

- **Lieberman et al. AJRCCM 2003:**
  - Of 100 adults admitted to hospital with asthma, 18 had evidence of acute *M pneumoniae* infection compared with 3% of controls

- **Johnston and Martin AJRCCM 2005:**
  - 12 studies investigated atypical bacteria (*M pneumoniae* and/or *C pneumoniae*) in acute asthma
  - nine supported a relationship between infection and acute asthma
Chlamydia pneumoniae

- Impairs mucociliary clearance and increases lung mucus production
- Chronic C pneumoniae infection may possibly cause lower airway inflammation
- **Cunnignham et al. ERJ 1998 & Miyashita JID 1995:** In school aged children as well as adults C pneumoniae has been linked to asthma exacerbations and may be a contributor to the chronicity of asthma
- Chronic chlamydial infections more common in children with higher rates of asthma exacerbations (increased susceptibility to other exacerbating stimuli ?)
- Allergy to the agent ? (IgE production)
Allergens
ALLERGEN-INDUCED RESPONSES FOLLOWING BRONCHOPROVOCATION

- Allergen-induced asthmatic responses
  - Early
  - Late
  - Dual
- Increase in airway responsiveness
- Airway inflammation
- Airway remodeling
ALLERGEN-INDUCED LAR
ALLERGEN-INDUCED AHR

Cockcroft, 1977
ALLERGEN-INDUCED AIRWAY INFLAMMATION

Sputum inflammatory cells before and after allergen inhalation

% Eosinophils

% Metachromatic Cells

n=12
p=0.04

p=0.01

Before 32 hours

Pin 1992
Virus infection and allergen exposure increase the risk of asthma hospital admissions in children

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Sensitised only</td>
<td>1.8 (0.4 to 9.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Virus only</td>
<td>3.8 (0.7 to 20.3)</td>
<td>0.11</td>
</tr>
<tr>
<td>Sensitised and exposed only</td>
<td>3.1 (0.97 to 9.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sensitised and virus only</td>
<td>12.3 (0.7 to 213.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Sensitised and exposed and</td>
<td>22.7 (4.6 to 112.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>virus detected</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On regular ICS</td>
<td>0.2 (0.1 to 0.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of asthma†</td>
<td>0.8 (0.7-0.9)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroids.
*Overall p value for the constructed variable is p<0.001. The reference category for the constructed variable is neither sensitised nor virus infected (+ exposed).
†Median (range) in years; OR refers to decreased risk with each additional year.

Murray Thorax 2006
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 (1.6–40.5)
- 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.
Occupational asthma is a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace.

Bernstein IL, Chan-Yeung M Malo JL, Bernstein DI. Asthma in the Workplace Marcel Dekker Inc., NY 1993
Asthma at the workplace

- Asthma \textit{caused} by workplace exposure (occupational asthma)
- Asthma \textit{exacerbated} by exposure at the workplace

- After latency period
- Without latency period

- « Irritant-induced asthma »
- or
- « Reactive airways dysfunction syndrome »

Variants of asthma
- e.g. non asthmatic eosinophilic bronchitis
OA - Pathogenesis

- Latency period (sensitization)
- Minimal exposure can lead to a severe bronchospasm
- Various mechanisms:
  - production of specific IgE (HMW substances)
  - lymphocyte activation or non immune mechanisms (LMW substances)
OUTCOME OF PC20 AND FEV1 AFTER ACUTE EXPOSURE TO CHLORINE *

Acute exposure

Inh Ster

Inh Ster

PC20 (mg/ml)

FEV1 (L)

TIME (days)

0 15 40 65 90 115 140

64

32

16

8

4

2

1

3

2

1

* see Lemière C et al. Eur Respir J 1997
Outdoor pollutants

- Particulate matter, ozone, nitrogen dioxide, sulfur dioxide and diesel exhaust—can increase airway inflammation and airway responsiveness

- Mechanisms?
  - free radical and oxidative stress
  - stimulation of the nocireceptor and autonomic NS
  - ciliary dyskinesis, epithelial damage, and increased pro-inflammatory mediators

- Possible synergy between pollutants and viral infection to cause asthma exacerbations
Ultrafine Particles
Particles < 0.1 micrometer diameter

Visible Dust 25-35 µm

Common Allergens 5-10 µm

Metallic Fumes 0.3-1 µm

Non-visible Dust 10-20 µm

Ultrafine Particles < 0.1 µm

Nano Particles < 0.02 µm

Human Hair ± 150 µm
Mean PM1 over 62 days at 12 locations on the MU soccer field

K. Rundell
Mean % changes in FEV\textsubscript{1} and FVC during and after walking for 2 hours in high or low air pollution environments

An ~3% change in FEV\textsubscript{1} per 10,000 UF particles/cm\textsuperscript{3} and an ~5% change per 10 µg/m\textsuperscript{3} PM\textsubscript{2.5} in FEF\textsubscript{25-75%} was also noted.

Change in lung function in healthy non-asthmatics after 30 min high intensity exercise

A. 

B.

Rundell et al 2008
Smoking and asthma

Increased symptoms and disability
Accelerated decline in FEV\textsubscript{1}
Reduced response to corticosteroids
Altered airway inflammation

Thomson N. JACI 2004
Tobacco smoke

- One of the most frequent exposures to an inhaled substance with adverse effects on the respiratory tract
- Smoking adds particles and gases to indoor air and is a major source of fine particles in the air
- Environmental tobacco smoke has been implicated in more severe RSV bronchiolitis, development of persistent wheezing, as well as asthma severity
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

Ulrik CS, Lange P. Cigarette smoking and asthma. Monaldi Arch Chest Dis. 2001
Siroux V, et al. Relationships of active smoking to asthma and asthma severity in the EGEA study. Eur Respir J 2000
Exercise-induced asthma

Change in FEV₁ (%)

Minutes post-exercise
Surfer’s asthma

Rachel U. Lee, M.D., Katharine M. Woessner, M.D., and David A. Mathison, M.D.

ABSTRACT

Common asthma triggers during recreational activities include allergen exposure, concomitant viral infection, and exercise. We present the case of a 42-year-old man with a 2-year history of wheezing, chest tightness, and upper respiratory symptoms that were associated with surfing. He denied symptoms with other forms of exercise and had no personal history of asthma. His physical exam was unremarkable and his pre- and postbronchodilator spirometry was normal. After detailed history and keen observation on the patient’s part, a diagnosis was made and he enjoyed good response to the therapy for this condition. Underrecognized asthma triggers and exposures in the recreational environment should be investigated.

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

- Viral infections and allergen exposure are the most common causes of asthma exacerbations.
- Non-viral causes of asthma exacerbation are common and should be recognized.
- A systematic evaluation of possible environmental causes should be done.
- For many of those, mechanisms of induction of AE remain to be studied but usually involve airway inflammation.
Increase in daytime symptoms is a sensitive and specific criterion for predicting corticosteroid-treated exacerbations in a clinical asthma trial

Dennis SM, Altmann DR, Lee TH
Clin Exp Allergy. 2005

**Background** To determine which diary card variables are the most predictive for administration of additional courses of corticosteroids using the TRUST (The Regular Use of Salbutamol Trial) data set.

**Methods** Logistic regression models were used to identify the extent to which a change in diary card variable affected the odds ratio (OR) for administering a course of oral or increased inhaled corticosteroids. The complete TRUST diary card data were used with over 200,000 days of diary card observations from 983 mild to moderate asthmatic subjects.

**Results** An increase in daytime symptoms of 1–5 U over baseline was associated with an increase in the OR for starting all types of corticosteroids from two- to 80-fold.

**Conclusions** These results indicate that an increase in daytime symptoms of two or more over baseline strongly predicts the administration of additional corticosteroids. The results have significant implications for both clinical practice and design of clinical trials in asthma.