Management of asthma
Global Initiative for Asthma Guidelines
Definition

- A chronic inflammatory disorder of the airways
- Many cells and cellular elements play a role
- Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing
- Widespread, variable, and often reversible airflow limitation
Burden of asthma

- One of the most common chronic diseases
  worldwide: estimated 300 million affected
- Prevalence increasing
- Children - 1% to 18%
- Major cause of school / work absence
- 1% of the total global disease burden

1. Masoli et al. *Allergy* 2004;59(5):469-78
Factors influencing asthma

Host Factors:

- **Genetic**
  - Atopy
  - IgE
  - Cytokine
  - Airway hyperresponsiveness
  - Chromosome 5

- **Gender**
  - Children < 14 year: M>F
  - Adult: F>M

- **Obesity**
  - Leptin

References:

Environmental factors

- **Indoor allergens** - mites, cockroaches, house dust
- **Outdoor allergens**
- **Occupational sensitizers** - Isocyanates, platinum salts, plants and animal products. High risk in farming and agricultural workers, painting, cleaning, plastic manufacturing
- **Air Pollution**
Factors influencing asthma

- Tobacco smoke - accelerated decline in lung function. 
  >4 times in infant of smoking mothers\textsuperscript{1}

- Respiratory Infections - RSV, Para influenza produce symptoms similar to asthma\textsuperscript{2}

\textsuperscript{1} Dezateux et al. *Am J Respir Crit Care Med* 1999;159(2):403-10
\textsuperscript{2} Sigurs et al. *Am J Respir Crit Care med* 2000;161(5):1501-7
Factors influencing asthma

- Measles protect against asthma\(^1\)
- Diet- breast feeding protect against asthma\(^2\)
- Hygiene hypothesis\(^3\)

History

- Recurrent episodes of wheezing
- Troublesome cough at night
- Cough or wheeze after exercise
- Cough, wheeze or chest tightness after exposure to airborne allergens or pollutants
- Colds “go to the chest” or take more than 10 days to clear
Cough variant asthma

- Chronic cough, more at night
- Variability in lung function or airway hyperresponsiveness
- D/D eosinophilic bronchitis

Other D/D
- ACE inhibitors
- GERD
- Post nasal drips
- Chronic sinusitis
- Vocal cord dysfunction
Exercise induced asthma

- 5-10 min after completing exercise
- Resolve spontaneously within 30-45 min
- Symptoms similar to asthma
- 8 min running protocol is used for diagnosis\(^1\)

Examination

- May be normal
- Usually *wheezing* on auscultation
- *Exacerbation* – cyanosis
  - drowsiness
  - difficulty in speaking
  - tachycardia
  - hyperinflated chest
  - use of accessory muscles
  - intercostal recession
Investigation

- Spirometry or peak expiratory flow
- Measurement of airway responsiveness
- Measurements of allergic status to identify risk factors
Pulmonary function test: diagnosis and monitoring

- **Reversibility**: improvement in FEV$_1$ or PEF measured within minutes after inhalation of SABA
  
  Significant: >12% and > 200ml
  not seen in all asthmatics

- **Variability**: increase or decrease in symptoms and lung function over time
  
  PEF >20% significant

  variability more important than reversibility
Measurement of airway responsiveness

- Methacholine, histamine, mannitol or exercise challenge test

  Fall in FEV$_1$ > 20% is diagnostic

Limitation: Limited specificity

  positive in allergic rhinitis, cystic fibrosis, bronchiectasis
  and COPD, fatal reaction

Non-invasive markers of airway inflammation

- Sputum eosinophil and neutrophil
- Exhaled nitric oxide\(^1\) and carbon monoxide\(^2\)

Allergic status: Skin test
Specific IgE

Alternative diagnosis

- Upper airway obstruction and Foreign body
- Hyperventilation syndrome and panic attack
- Vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Diffuse parenchymal lung diseases
- Left ventricular failure
New approach

- GINA 2006 emphasize asthma management based on *clinical control*
  rather than classification of patient by *severity*
- Introduction of concept of difficult to treat asthma
## Classification of asthma severity

<table>
<thead>
<tr>
<th>Classification</th>
<th>Symptoms</th>
<th>Nighttime symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1: Mild Intermittent</strong></td>
<td>$&lt; 2$/week then Asymptomatic</td>
<td>$&lt; 2$/month</td>
<td>FEV$_1$ or PEF $\geq 80%$ PEF var $&lt; 20%$</td>
</tr>
<tr>
<td><strong>Step 2: Mild Persistent</strong></td>
<td>$&gt;2$/wk, $&lt; 1$/day Activity affected</td>
<td>$&gt; 2$/month</td>
<td>FEV$_1$ or PEF $\geq 80%$ PEF var: 20-30%</td>
</tr>
<tr>
<td><strong>Step 3: Mod Persistent</strong></td>
<td>Daily symptoms Exacerb $\geq 2$/wk</td>
<td>$&gt; 1/$ week</td>
<td>60%$&lt;FEV$_1$&lt; 80% PEF var $&gt; 30%$</td>
</tr>
<tr>
<td><strong>Step 4: Sev Persistent</strong></td>
<td>Cont symptoms Frequent exacerb</td>
<td>Frequent</td>
<td>FEV$_1$ or PEF $&lt; 60%$ PEF var $&gt; 30%$</td>
</tr>
</tbody>
</table>
## 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 / “reliever” 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</td>
<td>1 in any week</td>
</tr>
</tbody>
</table>
Goals of successful management of asthma

- Achieve and maintain control of symptoms
- Maintain normal activity levels, including exercise
- Maintain pulmonary function as close to normal as possible
- Prevent asthma exacerbations
- Avoid adverse effects from asthma medications
- Prevent Asthma mortality
Asthma management

1. Develop patient/doctor partnership
2. Identify and reduce exposure to risk factors
3. Assess, treat and monitor asthma
4. Manage asthma exacerbations
5. Special considerations
Develop patient/doctor partnership

- Education
- Include the family and joint setting of goals
- Provide information about asthma
- Provide training on self-management skills
- Follow up and review
- Written action plan
- Improve adherence
Identify and reduce exposure to risk factors

- **Indoor allergens** – domestic mites, furred animals, cockroaches and fungi

- **Outdoor allergen** – pollens and molds

- **Indoor air pollutants** – primary / secondary smoke, nitric oxide, carbon monoxide, carbon dioxide, sulphur dioxide, formaldehyde

- **Outdoor air pollutants** – ozone, nitrogen oxides, acidic aerosols and particulate matter
Identify and reduce exposure to risk factors

- Occupational exposure
- Food and food additives
- Drugs: aspirin and NSAIDs
- Rhinitis, sinusitis and polyposis
- Obesity
- Emotional stress
Assess, Treat and Monitor Asthma

- Assessing level of asthma control
- Treating to achieve control
- Monitoring to maintain control
Treatment

- **Step 1:** as needed reliever medication
- **Step 2:** reliever medication plus a single controller
- **Step 3:** reliever medication plus one or two controllers
- **Step 4:** reliever medication plus two or more controllers
- **Step 5:** reliever medication plus additional controller option
TREATMENT STEPS

**REDUCE**

- STEP 1: asthma education
- STEP 2: environmental control

**INCREASE**

- STEP 3: as needed rapid-acting β₂-agonist

**SELECT ONE**

- STEP 4: low-dose ICS
- STEP 5: oral glucocorticosteroid (lowest dose)
- STEP 6: leukotriene modifier

**ADD ONE OR MORE**

- STEP 7: medium- or high-dose ICS
- STEP 8: leukotriene modifier
- STEP 9: anti-IgE treatment

**ADD ONE OR BOTH**

- STEP 10: low-dose ICS plus leukotriene modifier
- STEP 11: sustained-release theophylline

*Inhaled glucocorticosteroids
**Receptor antagonist or synthesis inhibitors
### Medications

<table>
<thead>
<tr>
<th>Controller</th>
<th>Reliever</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Inhaled glucocorticosteroids</td>
<td>- Rapid-acting inhaled β2-agonists</td>
</tr>
<tr>
<td>- Leukotriene modifiers</td>
<td>- Systemic steroids</td>
</tr>
<tr>
<td>- Long-acting inhaled β2-agonists</td>
<td>- Anticholinergics – ipratropium bromide and oxitropium bromide</td>
</tr>
<tr>
<td>- Systemic steroids</td>
<td>- Theophylline</td>
</tr>
<tr>
<td>- Theophylline</td>
<td>- Short-acting oral β2-agonists</td>
</tr>
<tr>
<td>- Cromones</td>
<td>- Long-acting oral β2-agonists</td>
</tr>
<tr>
<td>- Anti-IgE</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Low adult (μgm)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td><strong>Beclomethasone</strong></td>
<td>200-500</td>
</tr>
<tr>
<td></td>
<td>200-500</td>
</tr>
<tr>
<td><strong>Budesonide</strong></td>
<td>200-400</td>
</tr>
<tr>
<td></td>
<td>200-600</td>
</tr>
<tr>
<td><strong>Ciclosonide</strong></td>
<td>80-160</td>
</tr>
<tr>
<td><strong>Fluticasone</strong></td>
<td>100-250</td>
</tr>
<tr>
<td></td>
<td>100-250</td>
</tr>
</tbody>
</table>
Stepping down

- When controlled on medium- to high-dose inhaled glucocorticosteroids: 50% dose reduction at 3 month intervals\(^1\)

- When controlled on low-dose inhaled glucocorticosteroids: switch to once-daily dosing

- Maintain control at lowest possible step and lowest dose

- Controller treatment stopped if on lowest dose and no symptoms for 1 year

Use of combination rapid and long-acting inhaled β2-agonist and inhaled glucocorticosteroid in a single inhaler both as a controller and reliever is effective in maintaining a high level of asthma control and reduces exacerbations.

Temporarily doubling the dose of inhaled glucocorticoid-steroids is not effective. A four fold rise or more is equal to short course of oral steroids.

Difficult to treat asthma

- Insensitive to glucocorticosteroids
- Difficult to treat asthma from onset rather than progressing from milder asthma: poor compliance psychological psychiatric disorders
## Difficult asthma

Diseases that mimic asthma:

- COPD
- bronchiectasis, cystic fibrosis
- CHF – diastolic dysfunction
- upper airway obstruction
- aspiration or foreign body
- neuromuscular weakness
- vocal cord dysfunction
- hyperventilation / panic attack
Difficult to treat asthma

- Confirm the diagnosis

- Confirm compliance with treatment: incorrect or inadequate

- Consider current or past smoking: reduces effectiveness of steroids

- Comorbidities: chronic sinusitis
  - GERD
  - OSA
  - Psychological disorders
Manage Asthma Exacerbations

- Exacerbations are episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness.
- Characterized by decrease in expiratory airflow:
  - in PEF or FEV1
- Primary therapy: rapid acting bronchodilator
  - systemic steroids
  - oxygen supplementation
<table>
<thead>
<tr>
<th></th>
<th>mild</th>
<th>moderate</th>
<th>Severe</th>
<th>Respi. Arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>breathlessness</td>
<td>Can lie down</td>
<td>sitting</td>
<td>Hunch forward</td>
<td></td>
</tr>
<tr>
<td>Talk in sentences</td>
<td></td>
<td>phrases</td>
<td>words</td>
<td></td>
</tr>
<tr>
<td>alertness</td>
<td>May be agitated</td>
<td>Usually agitated</td>
<td>Usually agitated</td>
<td>Drowsy / confused</td>
</tr>
<tr>
<td>RR</td>
<td>increased</td>
<td>increased</td>
<td>&gt; 30/ min</td>
<td></td>
</tr>
<tr>
<td>Acc. Muscle / retraction</td>
<td>Usually not</td>
<td>usually</td>
<td>Usually</td>
<td>Paradoxical Abd move.</td>
</tr>
<tr>
<td>wheeze</td>
<td>Moderate</td>
<td>loud</td>
<td>Usually loud</td>
<td>absent</td>
</tr>
<tr>
<td>Pulse/ min</td>
<td>&lt;100</td>
<td>100-120</td>
<td>&gt; 120</td>
<td>bradycardia</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>absent</td>
<td>May be present</td>
<td>Often +</td>
<td>Absent due to fatigue</td>
</tr>
<tr>
<td>PEF- post bronchodilato</td>
<td>&gt;80%</td>
<td>60-80%</td>
<td>&lt;60% or response &lt;2hr</td>
<td></td>
</tr>
<tr>
<td>ŴPaO2(on air) or PaCO2</td>
<td>Normal &lt; 45mm Hg</td>
<td>&gt;60 mm Hg &lt;45mm Hg</td>
<td>&lt;60 mm Hg &gt;45 mm Hg</td>
<td></td>
</tr>
<tr>
<td>SaO2%</td>
<td>&gt;95%</td>
<td>91-95%</td>
<td>&lt;90%</td>
<td></td>
</tr>
</tbody>
</table>
Initial assessment

- History, examination, SpO$_2$, ABG (if PEF 30 – 50%)

↓

Initial treatment

- O2 to keep saturation >90% (children >95%)
- Inhaled SABA
- Systemic glucocorticosteroids (if no rapid response, pt is on oral steroids or severe episodes)
- Sedation contraindicated

↓

Reassess after 1 hr
<table>
<thead>
<tr>
<th><strong>Moderate episodes</strong></th>
<th><strong>Severe episodes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PEF 60 – 80% personal best</td>
<td>Risk factor for near fatal asthma</td>
</tr>
<tr>
<td>Moderate symptoms Accessory muscle use</td>
<td>PEF &lt;60%</td>
</tr>
<tr>
<td><strong>Treatment:</strong> O₂, inhaled β₂ agonist &amp; inhaled anticholinergics every 60min, oral steroids cont. Rx for 1-3 hrs</td>
<td>Severe symptom at rest, chest retraction</td>
</tr>
<tr>
<td></td>
<td>No improvement</td>
</tr>
<tr>
<td></td>
<td><strong>Treatment:</strong> O₂, Inhaled β₂ agonist &amp; anticholinergics, systemic steroids, I.V. MgSO₄</td>
</tr>
</tbody>
</table>

Reassess after 1-2 hrs
<table>
<thead>
<tr>
<th>Good</th>
<th>Incomplete</th>
<th>Poor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal O/E</td>
<td>Risk factor, mild to mod signs, PEF &lt; 60%, SpO2 &lt; 90%</td>
<td>Risk factors, drowsiness, confused, PEF &lt; 30%, PCO2 &gt; 45, PO2 &lt; 60</td>
</tr>
<tr>
<td>PEF&gt;70%, SpO2&gt;90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home treatment</td>
<td>Admit to acute care setting O2, β2 agonist, anti cholinergics, systemic steroids, I.V. MgSO4 Assess after 6-12 hr improve / not</td>
<td>Admit to intensive care O2, β2 agonist, anti cholinergics, systemic steroids, I.V. β2 agonist, I.V. theophyllines, intubation and mechanical ventilation</td>
</tr>
</tbody>
</table>
Criteria for discharge

- Post treatment FEV1 / PEF 40 – 60%
- Minimum of 7 day course of oral steroids
- Check inhaler technique
- Identify precipitating factors and strategies for future avoidance
Special situations

- **Pregnancy** - 1/3 worse
  - 1/3 less severe
  - 1/3 unchanged
  Poor control leads to increase perinatal mortality, prematurity and LBW

Monitored use of theophylline, inhaled steroids, β2 agonist and leukotriene modifiers are safe

Special situations

- **Surgery** -
  systemic glucocorticoids coverage during the surgical period and reduce rapidly 24hr after surgery for wound healing

- **Occupational asthma** -
  complete avoidance of the relevant exposure

- **Gastro esophageal reflux**

- **Aspirin-induced asthma** - avoid NSAIDS
Unstable asthma

- **Premenstrual asthma**: timing coincides with fall in progesterone secretion
  - Corticosteroid resistance
  - Mood disturbances
  - Altered β2 receptor dysfunction
  - Treat with i.m progesterone

- **Corticosteroid resistant**: ↑ in FEV1 < 15%
  - Despite 30 – 40 mg of steroids for 2 wks
  - Rx: Stop steroids, long acting β2 agonists, NF-κB inhibitor, p38MAP inhibitor, antioxidants, theophylline*

Unstable asthma

- **Brittle asthma**: 1. persistent and chaotic variability in PEF (40% diurnal for 50% time)
  2. sporadic sudden fall in PEF in well controlled

- **Treatment**: Type 1 – treat with β2 agonist terbutaline (3 – 12 mg in 24 hrs)
  Type 2 – due to food allergy – treat with adrenaline infusion or nebulisation

Newer therapies for asthma*

- **Ciclesonide**: metabolised locally
  - less systemic effects
  - improved safety margin
  - reduced airway response to adenosine

- **Theophylline**: PDE 4 inhibitor – selective
  - inhibits bronchoconstriction,
  - oedema, airway smooth muscle proliferation, excitatory non adrenergic, non cholinergic neurotransmission

Newer therapies for asthma*

- **Allergen immunotherapy / desensitisation**: 
  - Upregulation of TH1 cytokines
  - Downregulation of TH2 cytokines
  - Allergen derived peptide immunotherapy, immunostimulatory CpG oligonucleotide, DNA vaccines, mycobacterial vaccine
  - Have ↓ IgE binding and ↑ immunogenicity

- **Cytokine modulation strategies**— IL-10, IL-12, anti IL-5 antibody, IL-4 antagonist, IL-13 antagonist

- **Omalizumab** (anti IgE) — humanised monoclonal antibody against high affinity FcεR1 portion of IgE.
Conclusion

- Asthma can be effectively controlled by intervening to suppress and reverse inflammation as well as treating bronchoconstriction and related symptoms.

- Although there is no cure for asthma, appropriate management that includes a partnership between the physician and the patient/family most often results in the achievement of control.
All the best...