Asthma

Update - 2013

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Asthma

- A complex syndrome
- Multifaceted disease
- Heterogeneous
- Genetic and environmental determinants
Asthma is variable...

- ...in peak flow
- ...in risk factors
- ...in response to therapy
- ...in natural history
What Are The Therapeutic Targets?

Smooth muscle dysfunction
- Bronchoconstriction
- Bronchial hyper-reactivity
- Hyperplasia
- Inflammatory mediator release

Airway inflammation
- Inflammatory cell infiltration/activation
- Mucosal oedema
- Cellular proliferation
- Epithelial damage
- Basement membrane thickening

Symptoms \ exacerbations
Therapeutic Options

- Long-Term Control
  - Corticosteroids (inhaled, ICS)
  - Long-acting Beta$_2$-agonists (LABA)
  - Leukotriene antagonists (LTRA)
  - Theophylline
  - Others

- Quick Relief
  - Short-acting Beta$_2$-agonists (SABA)
  - Anti-cholinergics
  - Oral corticosteroids (exacerbations)
Inhaled Corticosteroids (ICS)

- ↓ Symptoms
- ↓ Frequency of severe exacerbations
- ↓ Risk of hospitalization
- ↓ Risk of death
- ➤ Improve or prevent deterioration of lung function
- ? (Reduces airway remodeling)

NAEPP, 1997; Donahue et al., 1997; Wennergren et al., 1996; Dompeling et al., 1993.
Relative Risk of Hospitalization in Adults and Children

Donahue et al., 1997.

\[ \beta_2 \text{-Agonists} \]

\[ \text{ICS plus } \beta_2 \text{-agonists} \]
Inhaled corticosteroids reduce the risk of asthma death **BUT** SABA alone may increase risk.

Suissa S et al. NEJM 2000;343:332-6

Role of ICS

- Should be used to control symptoms, prevent exacerbations/hospitalizations
- Prevent mortality
- Improve lung function
- Improve QOL
- Best used at low to moderate doses
Long Acting $\beta_2$-Agonists (LABA)

- Help relax airway smooth muscle
- Lasts at least 12 hours after single dose
- Used only in conjunction with anti-inflammatory therapy
- Formoterol vs. Salmeterol
How else do long-acting $\beta_2$-agonists improve asthma control?

- Reduces airway oedema by decreasing plasma leak
- Influence on airway sensory nerves
- Reduces mediator release from mast cells
- Reduces airways hyperresponsiveness
- Activation of corticosteroid receptors
Classes of $\beta_2$-agonists

<table>
<thead>
<tr>
<th>Speed of onset</th>
<th>Duration of action</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>fast</td>
<td>fast short</td>
<td>inhaled terbutaline, inhaled salbutamol</td>
</tr>
<tr>
<td>fast</td>
<td>slow long</td>
<td>inhaled formoterol</td>
</tr>
<tr>
<td>slow</td>
<td>fast short</td>
<td>oral terbutaline, oral salbutamol, oral formoterol</td>
</tr>
<tr>
<td>slow</td>
<td>slow long</td>
<td>inhaled salmeterol, oral bambuterol</td>
</tr>
</tbody>
</table>
Role of LABA

- As add-on therapy to ICS when a low to medium-dose of ICS alone fails to achieve control of asthma

- Should not be used as monotherapy in asthma
Oral Theophylline

- Inexpensive
- Corticosteroids have greater anti-inflammatory effect
- Less efficacious as add-on therapy than LABA
- Problems with side effects
- Still useful, esp. in moderate-severe asthma
Leukotriene Modifiers (LTRA)

- Interfere with activity of leukotrienes
- Currently available: zafirlukast, montelukast

**EFFICACY** COMPARED TO INHALED CORTICOSTEROIDS?

- Specific phenotypes respond better?
Who responds better to anti-leukotriene therapy?

- Younger, atopic patients
- Concomitant AR
- Aspirin sensitive patients
- Nasal polyposis
- Young, mild asthma with EIA
- Asthmatics who smoke?
Role of Leukotriene modifiers

- Mild asthma: as an alternative to low dose ICS

- Moderate/Severe asthma: add-on drug when ICS or combination therapy with ICS/LABA has not given desired effect
For optimal asthma management

- early recognition of poor asthma control
- early institution of anti-inflammatory treatment

are critical!
Why Have We Moved To Combination Therapy?

LABA + ICS
Rationale for Combination therapy

- Addition of a long-acting $\beta_2$-agonist is **better** in improving lung function and symptom control, reduces exacerbations

- Advocated by INTERNATIONAL & Local management guidelines (GINA, naepp, MOH CPG)

Greening et al, 1994
Woolcock et al, 1996
Pauwels et al, 1997
Ind PW et al, 1998
Rationale for Combination therapy

- Better improvement of Lung Function than ICS alone
- Control at Lower ICS Doses
- Rapid Control of asthma
- Better Prospects for Long-term Control
  - ? Potentially reduces airway remodelling
Combination therapy

(FP/Salmeterol): **Seretide**
(BUD/Formoterol): **SYMBICORT**

- newer inhaled formulations for the regular treatment of asthma
- Combine the **complementary actions** of ICS & long-acting $B_2$
  - anti-inflammatory
  - sustained bronchodilator activity
- Both drugs in a single inhaler
Complementary modes of action

Smooth muscle dysfunction
- Bronchoconstriction
- Bronchial hyper-reactivity
- Hyperplasia
- Inflammatory mediator release

Airway inflammation
- Inflammatory cell infiltration/activation
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- Basement membrane thickening

LABA

ICS

↓↓ Symptoms \ exacerbations
What does Asthma Control really mean?

- **New 2009 GINA guideline definition of control – A gold standard**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled (all of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daytime symptoms</strong></td>
<td>Twice or less per week</td>
</tr>
<tr>
<td>Limitations on activities</td>
<td>None</td>
</tr>
<tr>
<td>Nocturnal symptoms or awakenings</td>
<td>None</td>
</tr>
<tr>
<td>Need for reliever/‘rescue’ treatment</td>
<td>Twice or less per week</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal</td>
</tr>
</tbody>
</table>

GINA 2009
## Management approach based on control

**Step 1**
- Asthma education
- Environmental control

### Controller options

<table>
<thead>
<tr>
<th>Controller options</th>
<th>As needed rapid-acting β₂-agonist</th>
<th>As needed rapid-acting β₂-agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose inhaled ICS</td>
<td>Low-dose ICS plus long-acting β₂-agonist</td>
<td>Medium- or high-dose ICS plus long-acting β₂-agonist</td>
</tr>
<tr>
<td>Leukotriene modifier</td>
<td>Medium- or high-dose ICS</td>
<td>Leukotriene modifier</td>
</tr>
<tr>
<td>Low-dose ICS plus leukotriene modifier</td>
<td>Sustained release theophylline</td>
<td></td>
</tr>
<tr>
<td>Low-dose ICS plus sustained-release theophylline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In most cases, preferred controller option is an ICS/LABA combination

GINA 2009
When should you step down?

‘When Asthma control is maintained for at least 3 months, treatment can be stepped down with the aim of establishing the lowest step and dose of treatment that maintains control’
COMBINATION INHALERS FOR ASTHMA

**Seretide**
- **Seretide 500/50 µg**
  - 1 puff b.d.
- **Seretide 250/50 µg**
  - 1 puff b.d.
- **Seretide 100/50 µg**
  - 1 puff b.d.

**Symbicort**
- **160/4.5 µg**
  - 2-4 puff b.d.
- **160/4.5 µg**
  - 1 puff b.d.
- **160/4.5 µg**
  - 1 puff o.d.
Asthma control: fixed vs variable?

Conclusion

- At present, there is no evidence that better asthma treatment outcomes can be obtained by moment-to-moment symptom-driven use of ICS/LABA therapy compared with conventional physician-monitored and adjusted ICS/LABA therapy

Chapman KR et al. Thorax 2010
Patient Education & monitoring

- Critical in any chronic disease
- Compliance issues
- Inhaler technique
- Avoid trigger factors
- **Asthma action plan**
- Need for regular follow-up
- Disease prevention, health promotion
Written Asthma Action Plan

- ↑ Overall asthma control
- ↓ Severe exacerbations
- ↓ Hospitalization - 83%
- ↓ EMD visits - 78%
- ↓ Costs
- ↓ Mortality - 70%

Adams et al Respirology 2001 6:297
Abramson et al AJRCCM 2001 163:12
<table>
<thead>
<tr>
<th>ZONE</th>
<th>GREEN</th>
<th>YELLOW</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good Control</td>
<td>Asthma Getting Worse</td>
<td>Asthma is Severe</td>
</tr>
</tbody>
</table>

### Symptoms

- **GREEN**
  - No wheeze/ coughing night / day
  - Perform all activities
  - Sleep well
  - Peak flow >80% best

- **YELLOW**
  - Any wheeze /cough/ shortness of breath/chest tightness day/night
  - Usual activities affected
  - Sleep disturbed
  - Peak flow <80% best

- **RED**
  - Cannot talk / walk
  - Unable to sleep
  - Use of reliever < 3 hourly, little response of symptoms to reliever
  - Peak flow <60% best

### What You Should Do

- **GREEN**
  - Continue usual medications
    - Preventer
      - __________ Dose___
    - Reliever
      - __________ Dose___
    - Other medications

- **YELLOW**
  - Increase usual medications
    - Preventer
      - __________ Dose___
    - Reliever
      - __________ Dose___
    - Other medications

- **RED**
  - SEEK EMERGENCY TREATMENT
    - Go to the nearest clinic / A&E
    - Call ambulance 995 IF YOU HAVE
    - Severe shortness of breath, or unable to speak comfortably, or blueness of the lips / fingers
    - CONTINUE Reliever
      - __________ Dose___
    - stat dose medication________ until you reach hospital

*If you respond, continue this regime for 1 week, then return to the green zone regime.*

*If you do not respond within 60 minutes **GO TO THE RED ZONE!**

*If you need reliever >1x/week for more than 1 month, you should get an earlier*
Monitoring Strategy

- Identify and avoid triggers
- Achieve control by selecting appropriate medication (± spacer device) - Step approach
- Treat asthma attacks promptly & effectively
- Educate patients to manage their condition
- Monitor ASTHMA CONTROL (ACT score) to maintain effective long-term control
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?  

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. During the past 4 weeks, how often have you had shortness of breath?  

<table>
<thead>
<tr>
<th>More than once a day</th>
<th>Once a day</th>
<th>3 to 6 times a week</th>
<th>Once or twice a week</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night, or earlier than usual in the morning?  

<table>
<thead>
<tr>
<th>4 or more nights a week</th>
<th>2 or 3 nights a week</th>
<th>Once a week</th>
<th>Once or twice</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?  

<table>
<thead>
<tr>
<th>3 or more times per day</th>
<th>1 or 2 times per day</th>
<th>2 or 3 times per week</th>
<th>Once a week or less</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

5. How would you rate your asthma control during the past 4 weeks?  

<table>
<thead>
<tr>
<th>Not controlled at all</th>
<th>Poorly controlled</th>
<th>Somewhat controlled</th>
<th>Well controlled</th>
<th>Completely controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
Using the ACT score...practical application

<table>
<thead>
<tr>
<th>ACT score</th>
<th>Level of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 25</td>
<td>Good</td>
</tr>
<tr>
<td>15 - 19</td>
<td>Inadequate</td>
</tr>
<tr>
<td>10 - 14</td>
<td>Poor</td>
</tr>
<tr>
<td>5 - 9</td>
<td>Very Poor</td>
</tr>
</tbody>
</table>

MANAGEMENT OF ASTHMA TO ACHIEVE CONTROL

Assess control at each visit with the Asthma Control Test (ACT)

ACT score $\geq 20 \rightarrow$ Maintain or step down

ACT score $< 20 \rightarrow$ Step up

Step 5: Refractory asthma $\rightarrow$ Refer for further evaluation
Step 4: Medium or high dose ICS plus one or more “add on drug/s”
Step 3: Low dose ICS plus one “add on drug”
Or Medium to high dose ICS
Step 2: Low dose ICS
Step 1: As needed reliever and/or controller
Is this the end?

New drug classes in development:

- Phosphodiesterase-4 inhibitors
- IL-5, IL-13 antagonists
- CCR3 antagonists
- Adhesion molecule blockers
- Anti-IgE therapy - now available
- New immuno-modulators
Asthma vs COPD

Table 1  Clinical features of COPD and bronchial asthma

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking history</td>
<td>Nearly all</td>
<td>Possibly</td>
</tr>
<tr>
<td>Symptoms &lt; 35 years</td>
<td>Rare</td>
<td>Often</td>
</tr>
<tr>
<td>Chronic productive cough</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>Persistent/progressive</td>
<td>Variable</td>
</tr>
<tr>
<td>Nocturnal symptoms</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Diurnal variation of symptoms</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
</tbody>
</table>
2013 Update -
Key Changes in the Guidelines

1. Shift from Classification of Asthma Disease Severity to Asthma Control
2. Use of Written Self-Management Plans
3. An objective assessment of Asthma Control (ACT score)
4. Treatment based on Control
Summary

• Emphasis now on clinical control

• Develop an asthma action plan

• More preventer, less reliever

• MOH CPG recommends ACT monitoring to maintain control
  – The ACT is a practical and robust tool that provides a composite measure of asthma control
  – Can be done by asthmatics themselves (at zero cost)
  – Scores may be used as a treatment target
Thank You

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