Predicting, Preventing and Managing Asthma Exacerbations

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University of Cape Town
South Africa
Asthma exacerbations

- **Predicting exacerbation**
  - recognising loss of control, risk/s for exacerbation

- **Preventing exacerbation**
  - early, effective treatment

- **Treating exacerbation**
  - treatment strategies
What is an exacerbation?

- **severe exacerbation** - event requiring urgent action to prevent a serious outcome, eg hospitalization or death
- **moderate exacerbation** - troublesome to patient, need a change in treatment, but not severe
- **mild exacerbation** – just outside normal range of variation; can’t distinguish from transient loss of asthma control

*ATS/ERS Task Force, AJRCCM 2009;180:59-99*
What is an exacerbation?

- **severe exacerbation**
  - require systemic steroids
  - emergency visit or hospitalization

- **moderate exacerbation**
  - requires a temporary change in treatment
  - increase in ICS

- **severity more difficult to measure in child**
  as parental report, no PFT

*ATS/ERS Task Force, AJRCCM 2009;180:59-99*
Asthma control & severity

- **Asthma control** - extent to which asthma manifestations have been removed with treatment
  - clinical control (symptoms, QOL)
  - future risk – loss of control, exacerbations, decline in PFT, drug side effects
  - phenotype switch from episodic (viral) to multi-trigger is a component of risk

- **Asthma severity**
  - Difficulty in controlling asthma with therapy

ATS/ERS Task Force, AJRCCM
2009;180:59-99
## Levels of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled</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>3 or more features of partly controlled asthma present in any week</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</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>

2006 www.ginasthma.org
## Treatment Steps

### Reduce

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
</tr>
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<tbody>
<tr>
<td><strong>Controller Options</strong></td>
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<tr>
<td>as needed rapid-acting β₂-agonist</td>
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<td>low-dose ICS</td>
<td>oral glucocorticosteroid (lowest dose)</td>
<td></td>
</tr>
<tr>
<td>SELECT ONE</td>
<td>SELECT ONE</td>
<td>ADD ONE OR MORE</td>
<td>ADD ONE OR BOTH</td>
<td></td>
</tr>
<tr>
<td>low-dose ICS*</td>
<td>low-dose ICS plus long-acting β₂-agonist</td>
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<td>medium- or high-dose ICS</td>
<td>leukotriene modifier</td>
<td>anti-IgE treatment</td>
<td></td>
</tr>
<tr>
<td>low-dose ICS plus leukotriene modifier</td>
<td>sustained-release theophylline</td>
<td>low-dose ICS plus sustained-release theophylline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *inhaled glucocorticosteroids
** receptor antagonist or synthesis inhibitors
TREATMENT STEPS

<table>
<thead>
<tr>
<th>STEP</th>
<th>CONTROLLER OPTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>as needed rapid-acting (\beta_2)-agonist</td>
</tr>
<tr>
<td>2</td>
<td>low-dose ICS* or leukotriene modifier**</td>
</tr>
<tr>
<td>3</td>
<td>low-dose ICS or medium- or high-dose ICS</td>
</tr>
<tr>
<td>4</td>
<td>low-dose ICS plus leukotriene modifier</td>
</tr>
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<td>5</td>
<td>low-dose ICS plus sustained-release theophylline</td>
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- *inhaled glucocorticosteroids
- **receptor antagonist or synthesis inhibitors

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<td>anti-IgE treatment</td>
</tr>
<tr>
<td>STEP 1</td>
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**Reduce**

- as needed rapid-acting β₂-agonist

**Increase**

- as needed rapid-acting β₂-agonist

**Controller Options**

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<th>Step</th>
<th>Reducing Options</th>
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<th>Adding Options</th>
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<tbody>
<tr>
<td>1</td>
<td>Asthma Education</td>
<td>Environmental Control</td>
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<th><strong>Add One or Both</strong></th>
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*Inhaled glucocorticosteroids
**Receptor antagonist or synthesis inhibitors
PREDICTING asthma exacerbations

◆ degree of control
  – severe exacerbations more common with poorly controlled asthma but also in mild or well controlled
  – dissonance between control & exacerbations

◆ current poor control predicts future loss of control, health care utilisation

◆ no reliable well tested methods for early detection in children

◆ available measures (PFT, NO, eos sputum, diary cards etc) not useful for predicting exacerbation, Covar JACI 08, Sorkness JACI 2007,08
HOST factors - asthma exacerbations

- Control
  - prior exacerbation more likely to repeat exacerbation
- Genetic predisposition – innate immunity polymorphisms, TLR8, CD14, filaggrin null mutation
- Atopy
- Co-morbid conditions
- Adherence
- Psychosocial
ENVIRONMENTAL factors - asthma exacerbations

- **viral infections**
  - rhinovirus infection
- **interaction with sensitisation & allergen exposure**
- **seasonal patterns exacerbation** – viral infection, aeroallergen, reduced adherence  
  (*Sears, 2007*)
- **passive smoke exposure**
- **gene-environment interactions**
Predictors of asthma exacerbations in preschool children

- post hoc analysis 689 children 2-5 yrs on montelukast vs placebo 12 yr study
  - 196 (28%) had exacerbation
- no individual symptom predictive of exacerbation
- combination of increased daytime cough, daytime wheeze & night time B2 use 1 day before exacerbation predictive of exacerbation – 67%

exacerbations Swern Ann Allergy, Asthma, Immunol 2008
PREVENTION & TREATMENT of asthma exacerbation

- Asthma education
- Delivery systems for inhaled therapy
- Corticosteroids – inhaled, oral
- Combination therapy
- Leukotriene receptor antagonist (LTRA)
Asthma education

- Educational intervention to parent / child with emergency visit for child asthma reduces:
  - ER visits for exacerbations [RR 0.73 95% CI, 0.65–0.81]
  - admission [RR 0.79 95% CI, 0.69–0.92]
  - unscheduled doctor visit [RR 0.68 95% CI, 0.57–0.81]

Boyd M et al Cochrane Database 2009
Written action plan – symptoms

- symptom-based action plans superior to PF-based action plans in children and adolescents getting asthma education and regular medical review

- children using symptom-based written action plans had lower risk of exacerbations requiring acute care visits [RR 95% CI, 0.73; 0.55–0.99]

What delivery system ??
Bronchodilator ($\beta_2$) – MDI vs nebuliser

- delivery better via MDI + spacer vs nebuliser
  - more lung delivery, less side effects, *Cates Cochrane 06*
  - meta analysis 6 studies, 491 kids acute asthma in ER, *Castro-Rodriguez JA, J Peds 2004*
  - MDI reduced hospitalisation (OR, 0.42; 95% CI, 0.24–0.72)
  - even more in moderate-to-severe exacerbation (OR, 0.27; 95% CI, 0.13–0.54)
- 4 - 10 puffs via MDI-spacer similar efficacy to single nebulizer treatment, *Schramm Curr Opinion Peds 2009*
Choosing an inhaler device for children

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Preferred Device</th>
<th>Alternate Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger than 4 years</td>
<td>Pressurized metered-dose inhaler <em>plus</em> dedicated spacer with face mask</td>
<td>Nebulizer with face mask</td>
</tr>
<tr>
<td>4 – 6 years</td>
<td>Pressurized metered-dose inhaler <em>plus</em> dedicated spacer with mouthpiece</td>
<td>Nebulizer with mouthpiece</td>
</tr>
<tr>
<td>Older than 6 years</td>
<td>Dry powder inhaler, <em>or</em> breath-actuated pressurized metered-dose inhaler, <em>or</em> pressurized metered-dose inhaler with spacer and mouthpiece</td>
<td>Nebulizer with mouthpiece</td>
</tr>
</tbody>
</table>
Low cost vs commercial spacer

- **Similar efficacy** for bronchodilators in acute asthma
  - 6 trials, 658 participants
  - no difference in hospitalisation, change in oxygen saturation, PEFR, clinical score or need for additional treatment, *Rodriguez, Cochrane Database 2008*
Preventing & Treating Exacerbation

- Corticosteroids
  - high dose ICS
  - short course oral steroids
- Combination therapy
- LTRA
  - add-on for seasonal
  - intermittent, pre-emptive
Inhaled corticosteroids

- Does increasing dose of ICS at start of exacerbation reduce severity or prevent progression???
  - double dose not effective
  - 4 x dose for 7 days may be effective, reducing need for oral steroids — Volovitz Respir Med 2007
High dose inhaled corticosteroids

- 4 RCT ICS vs placebo of high dose ICS at time of exacerbation
- budesonide – 400-800ug at 30min intervals x 3 plus albuterol Volovitz Respir Med 2007, Devidayal 1999, Singhi 1999
- shortened ER stay, reduced hospitalisation, reduced need for oral steroids
Pre-emptive high-dose fluticasone for virus induced wheeze in young children

- Children 1-6yrs with recurrent viral induced wheeze
  - 750ug BD fluticasone / placebo bd at onset of URI till symptoms resolved x 48 hrs
  - 10 days over 6-12 months
- Primary outcome: rescue with oral steroids
- Secondary outcomes: use of β2-agonists, acute care visits, hospitalizations, discontinuation of the study drug, change in growth, bone mineral density

Ducharme FM, NEJM 2009
Pre-emptive high-dose fluticasone

- less use of rescue oral steroids in fluticasone
  - 8% vs 18%, OR 0.49 (0.30-0.83)
- symptoms milder and shorter, fewer days of albuterol in fluticasone grp
- fluticasone grp - smaller height ($z$ score -0.24; -0.4 to -0.08) and weight gain
- no differences between groups in basal cortisol level, bone mineral density, or adverse events
- not recommended until long term S/E clarified

*Ducharme FM, NEJM 2009*
Oral corticosteroids – short course?

- Short courses as effective as longer
- RCT of 3 vs 5-days of oral prednisolone in 201 children discharged from ER with exacerbation, *Gordon Ped Emerg Care* 2007
  - 2-week follow up, no significant differences in clinical asthma score, cough score or QOL
- 2 other studies of single-dose dexamethasone therapy (0.6 mg/kg) vs 5-day oral prednisone (2 mg/kg/day), *Altamini Ped Emerg Care* 2006, *Warner Ped Pulm* 1998
  - No difference in clinical acute or 2 week f/up outcome
Combination therapy (ICS/ LA B$_2$) for maintenance & relief

- complimentary actions at molecular level, co-deposition
- ease, convenient, simple, better adherence
- ensures concomitant use of ICS
- formoterol/ budesonide – rapid onset action
  formoterol
Combination therapy for maintenance and relief

- subset of 341 children (4-11 yrs) with moderate to severe asthma uncontrolled on ICS & at least 1 exacerbation in past yr
  - mean pre-bronchodilator FEV1 76%
  - mean daily ICS 315 mcg/day

- **bud/formoterol 80/4.5 mcg nocte + terbutaline or + bud/ form for relief**
  - or bud 4x dose (320mcg) vs terbutaline

*Bisgaard et al, Chest 2006*
<table>
<thead>
<tr>
<th>Months</th>
<th>Budesonide/ formoterol for maintenance and relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>BUD 320 µg od³ + terbutaline 0.4 mg for relief</td>
</tr>
<tr>
<td>1-3</td>
<td>Fixed-dose BUD</td>
</tr>
<tr>
<td>3-6</td>
<td>BUD/FORM 80/4.5 µg od³ + terbutaline 0.4 mg for relief</td>
</tr>
<tr>
<td>6-9</td>
<td>Fixed combination</td>
</tr>
<tr>
<td>9-12</td>
<td>BUD/FORM 80/4.5 µg od³ + BUD/FORM 80/4.5 µg for relief</td>
</tr>
<tr>
<td></td>
<td>SMART</td>
</tr>
</tbody>
</table>
Combination therapy maintenance + terbutaline vs combination for relief

- **Large reduction in hospitalisation**, OR 0.06 (0.00 to 1.10) – but ? chance (small no. events)
  - 7 hosp in terbutaline grp, 1 asthma SAE in bud/form
- **Number of children with exacerbations requiring oral corticosteroids not reported**
- **Less use of relievers in bud/form** (reduced 0.28 puffs per day (95% CI -0.54 to -0.02)
- **No diff in asthma control days, annual growth, change lung function**

*Cates Cochrane Database 2009*
Combination for maintenance & relief vs high dose ICS for maintenance

- 224 children (bud/form vs 4x bud)
- decrease in severe exacerbations requiring doctor visit or oral steroids, OR 0.33 [0.15, 0.77] in bud/form
- no difference in hospitalisation (but 0 in bud/form, 1 in ICS)
- no diff in SAEs
- steroid load lower in bud / form
  - mean daily dose (126ug vs 320ug)
  - less days on oral steroids (32 versus 141 days)
  - mean increase in height greater 5.3 cm (bud/form) vs 4.3 cm (bud)

Cates Cochrane Database 2009
LTRA add-on for prevention of seasonal exacerbations

- RCT montelukast vs placebo + usual therapy in 194 children 2-14 yrs from Sept to mid Oct in N America
  - 53% reduction in days with asthma symptoms
  - 78% reduction in unscheduled doctor visits
- occurred in those on and off ICS
- occurred in those with/ out URI

Johnston Peds 2007
Pre-emptive use of LTRA for prevention exacerbations

- RCT montelukast vs placebo x 7 days or till symptoms resolved x 48 hrs
  - 220 children 2-14 yrs with intermittent asthma at first sign of URI/asthma symptoms
- Reduced emergency room visits OR 0.65 (0.47–0.89)
- No significant reduction in hospitalizations, duration of episode, symptoms
- No difference in oral steroid use

Robertson AJRCCM 2007
Conclusions - preventing exacerbations

- Education, written action plan based on symptoms
- Attention to and avoidance of triggers - smoke
- Good control – ICS best
- Combination therapy for maintenance and relief reduces exacerbations – only 1 study, limited data
- LTRA addition for seasonal exacerbations
- LTRA intermittent for viral induced – only effect on ER visits
Conclusions - treating exacerbations

- Early recognition of loss of control or viral URI
- 4x dose ICS – may prevent progression, but potential for side effects (height)
- Treatment
  - inhaled therapy with MDI-spacer optimal
  - B2 + high dose ICS
  - combination therapy – formoterol - promising
  - oral steroids – short course