Management of Asthma & wheeze in children: cases

To respond to a question, click the letter corresponding to the answer. To change answer press << then re-enter letter.
Management of asthma and wheeze in children

Philip Pattemore

Achieving clarity

Mt Tasman & Mt Cook from Hokitika Beach
In what text did the word “asthma” first appear?

- As panting breath
  - Homer speaks about a warrior who died at the end of a furious battle—"with asthma and perspiration"

- As a symptom
  - Writings of the School of Hippocrates

- As a condition
  - Aretaeus of Cappadocia 1 A.D.

  "If from running, gymnastic exercises, or from any other work, the breathing becomes difficult it is called asthma."
Asthma management of old

- Inhaling belladonna on hot bricks – ancient Egypt
- Eating elephant or crocodile dung – ancient Egypt
- Chinese herbs containing pseudoephedrine – ancient China
- Relaxation - Seneca
- Smoking Datura - India 100 AD
- Owl’s blood in wine – Galen
- Moderation, and chicken soup – Maimonides
- Coffee – Robert Bree 1797
- Asthma cigarettes (stramonium) – India and Britain 1800-1950’s
- Siegel’s steam spray inhaler – 1867
- Khella plant – late 1800’s eastern Mediterranean
  - (cromoglycate and amiodarone are analogs of Khellin)
- Anti-depressive psychotherapy – 1930s
Asthma drugs in the 1900s

- 1903 Epinephrine injection
- 1910 Epinephrine given by squeeze bulb inhaler
- 1911 Desensitisation
- 1930’s Aminophylline and theophylline
- 1944 Cortisol
- 1946 Antihistamines
- 1949 Aerohaler (first DPI)
- 1956 Medi-haler-Epi (epinephrine), and Iso (isoprenaline) (Riker)
- 1960’s Triamcinolone, Ventolin Rotacap,
- 1968 Intal Spinhaler, Albuterol inhaler
- 1960’s-72 Becotide inhaler (not widely used until 1972)
- 1987 Ipratropium bromide
- 1990’s Combivent
- 1994 Salmeterol
- 1993 Fluticasone, budesonide
- 1998 Montelukast
- 1998 Seretide
- 2000 Symbicort
- 2002 Omalizumab (anti-IgE monoclonal)
How would you diagnose Ben?

**Best rapid Gestalt**

- Ben, a 6 month old boy, is admitted to hospital with acute wheezing and difficulty breathing in winter
- Previously admitted for bronchiolitis at 3m. Mother non-smoker, but has asthma. The child has flexural atopic eczema
- Auscultation: wheeze, no crackles
- Viral PCR is +ve for RSV

A. Bronchiolitis
B. Transient infant wheeze
C. Asthma
D. Virus-triggered wheeze
E. Something else
Defining bronchiolitis: US versus us

- **US bronchiolitis**
  - Acute viral URTI with wheezy illness in children under 2 years
  - US infants can’t get asthma, by definition

- **European/British/Australasian bronchiolitis**
  - Acute wheeze with inspiratory crackles under 2y / 1y / 6m of age
  - Lakhanpaul et al. [http://www.nottingham.ac.uk/paediatric-guideline/breathingguideline.pdf](http://www.nottingham.ac.uk/paediatric-guideline/breathingguideline.pdf)
Bronchioles
Interstitium
Fine Crackles
Modified Asthma Predictive Index

<table>
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<th>mAPI</th>
<th>m2API</th>
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<td><strong>Primary</strong></td>
<td>≥4 wheezing episodes in a year</td>
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<td><strong>AND</strong></td>
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<td><strong>Secondary</strong></td>
<td>At least 1 major:</td>
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<tr>
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<td>Parental physician-diagnosed asthma</td>
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<td>Physician-diagnosed atopic dermatitis</td>
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<tr>
<td></td>
<td>Allergic sensitization to at least one aeroallergen</td>
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</tbody>
</table>

OR

At least 2 minor:

- Wheezing unrelated to colds
- Eosinophils ≥4% in circulation
- Allergic sensitization to milk, egg, or peanuts
Asthma diagnosed %

- m2API Positive
- m2API Negative

Asthma diagnosed %

Age at prediction

0
1
2
3
6 years
8 years
11 year
1
2
3

Diagnosis of asthma

“...diagnosing pre-school children is difficult and often results in undertreatment of asthmatics and overtreatment of transient wheezers...”

Explaining a “risk of asthma”

- “Ben has had two episodes of wheeze, and I’m sure you’re wondering whether he has asthma like you do.
- “He does have significant risk factors for asthma – his eczema and the family history. Whether he follows in this way will become clearer over time.
- “In the meantime he may develop further episodes of wheeze so it is important to see if a reliever helps him, and if so, to give you an action plan and advice about using a spacer. Smoking exposure should be avoided.
- “If he develops more wheezing without colds…”
How would you treat Ben?

- Ben is 9 months old and has now had 4 admissions for wheezing. In addition he has had regular wheezing and shortness of breath in cold weather, and when he is excited or crawling. He is waking several times a week with wheezing.

A. Just intermittent

B. Daily montelukast

C. Daily inhaled steroids

D. Daily oral steroids

E. Pre-emptive inhaled steroids prn

rescue salbutamol or ipratropium
37 infants with wheeze or cough and atopic background

Figure 1  Changes in scores between run in and weeks 11–12. *p < 0.05.

Mean daily symptom score

Placebo
Fluticasone

Period
Run in Wk 1–2 Wk 3–4 Wk 5–6 Wk 7–8 Wk 9–10 Wk 11–12

Daily ICS and exacerbations needing oral steroids in pre-school children

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**Figure 1:** Relative risk of patients with exacerbations needing rescue oral corticosteroids

Daily ICS and asthma-free days in pre-school children

Figure 2: Mean group difference of percentage of asthma-free days


- A Daily ICS vs placebo
  - Guibert (2007)
  - Papi (2009a)
  - Subtotal
  - Mean difference (95% CI): -5.52 (-8.81 to 2.22)

- B Daily ICS vs pre-emptive ICS
  - Papi (2009)
  - Zeiger (2011)
  - Subtotal
  - Mean difference (95% CI): -1.23 (-4.32 to 1.86)

- C Daily LTRA vs placebo
  - Valovirta (2011a)
  - Mean difference (95% CI): -1.10 (-2.26 to 0.06)

- D Daily LTRA vs pre-emptive LTRA
  - Valovirta (2011a)
  - Mean difference (95% CI): -1.40 (-2.59 to -0.21)

BMD 800 µg prn vs BMD 400µg bd
BUD 1000µg bd x 7d vs 500 µg daily
How would you treat Dan?

- Ben’s brother Dan, 3 yrs old, has intermittent episodes of wheezing with infections requiring admission 6 times in the last year. He has no interval symptoms

A. Intermittent bronchodilators & oral steroids
B. Pre-emptive high dose inhaled steroids
C. Daily inhaled steroids
D. Daily montelukast
E. Daily oral steroids or Other
Pre-emptive ICS and risk of exacerbations needing oral steroids in pre-school children

**Figure 3: Pooled relative risk of patients with exacerbations needing rescue oral corticosteroids**

- **A Pre-emptive ICS vs pre-emptive LTRA**
  - Bacharier (2008)
  - Relative risk (95% CI): 0.82 (0.59-1.15)
  - BUD 1000 µg bd x 7d
  - FP 750 µg bd x 10d max
  - BUD 1600 µg/d x 3d
  - then 800 µg/day x 7d

- **B Pre-emptive LTRA vs placebo**
  - Bacharier (2008)
  - Relative risk (95% CI): 0.68 (0.53-0.86)

Early ICS in ED vs placebo: effect on hospital admission in children

Early ED use of ICS vs oral steroids: effect on hospital admission in children

- FP 500µg 33
- BUD 800µg x3
- TAC 600µg
- BUD 2000
- DEX 1.5 mg/kg
- FP 250µg x8
- FP 250µg x8
- BUD 1600µg

Montelukast in 549 preschoolers

Figure 4. Kaplan-Meier estimate of the time to first asthma exacerbation

Montelukast in 549 preschoolers

Montelukast in 1771 pre-schoolers

**Figure 4-1a. Stepwise Approach for Managing Asthma in Children 0–4 Years of Age**

- **Persistent Asthma: Daily Medication**
  - Consult with asthma specialist if step 3 care or higher is required.
  - Consider consultation at step 2.

- **Step 1**
  - Preferred: Medium-dose ICS
  - Alternative: SABA PRN
  - Cromolyn or Montelukast

- **Step 2**
  - Preferred: Medium-dose ICS
  - Alternative: SABA PRN
  - Cromolyn or Montelukast

- **Step 3**
  - Preferred: High-dose ICS + either LABA or Montelukast
  - Oral systemic corticosteroids

- **Step 4**
  - Preferred: High-dose ICS + either LABA or Montelukast
  - Oral systemic corticosteroids

- **Step 5**
  - Preferred: High-dose ICS + either LABA or Montelukast
  - Oral systemic corticosteroids

- **Step 6**
  - Preferred: High-dose ICS + either LABA or Montelukast
  - Oral systemic corticosteroids

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**Patient Education and Environmental Control at Each Step**

- **Quick-Relief Medication for All Patients**
  - SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms.
  - With viral respiratory infection: SABA q 4–6 hours up to 24 hours (longer with physician consult). Consider short course of oral systemic corticosteroids if exacerbation is severe or patient has history of previous severe exacerbations.
  - Caution: Frequent use of SABA may indicate the need to step up treatment. See text for recommendations on initiating daily long-term-control therapy.
Two patterns of asthma

- Rhinovirus
- Parainfluenza virus
- Rhinovirus

- Exercise
- Night
- Cold air
- Dust
Asthma classification

**INTERMITTENT EPISODIC VIRAL**

- Attacks require reliever only
- Attacks usually require GP
- Attacks often require hospital
- Life-threatening: Has required CPR, IV, ICU or ventilation

**PERSISTENT MULTITRIGGER**

- Minimal lifestyle disruption
- Exercise or sleep disrupted weekly
- Exercise, sleep disrupted daily
  +/− schooling, socialisation, growth
Asthma management

**INTERMITTENT EPISODIC VIRAL**

- Reliever and spacer education
- Reduce viral exposure
  - Reduce smoke exposure
- Good action plan
  - Join S+ John ambulance
- Selected cases Pre-emptive-ICS, ICS, LTRA

**PERSISTENT MULTITRIGGER**

- Reliever, spacer, education and advice as for intermittent
- Inhaled steroids
- Check compliance, spacer, technique
- Consider LABAs
- Consider montelukast
How would you assess Ben’s asthma? Choose the most informative measure

- Ben, now 8, has ongoing symptoms and exacerbations and multiple allergies
- He is currently taking fluticasone 125 µg ii bd and his compliance and spacer technique are excellent

A. Normal history: parents & Ben
B. Symptom Diary
C. PEF Diary
D. Child-Asthma Control Test
E. Other
# Jason's Asthma Diary

**Month:** August

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<th>Week Two</th>
<th>Week Three</th>
<th>Week Four</th>
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<td>✓</td>
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<td>Mild – active sport affected by asthma</td>
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<td>✓</td>
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<tr>
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<td>GP Visit</td>
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<td>Prednisone</td>
<td>20</td>
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<td>20</td>
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<td>Missed school (if applicable)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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**Comments/Triggers:**

- [cat]

See instructions on the other side.
Childhood Asthma Control Test

Have your child complete these questions.

1. How is your asthma today?
   - Very bad (0)
   - Bad (1)
   - Good (2)
   - Very good (3)

2. How much of a problem is your asthma when you run, exercise or play sports?
   - It's a big problem, I can't do what I want to do. (0)
   - It's a problem and I don't like it. (1)
   - It's a little problem but it's okay. (2)
   - It's not a problem. (3)

3. Do you cough because of your asthma?
   - Yes, all of the time. (0)
   - Yes, most of the time. (1)
   - Yes, some of the time. (2)
   - No, none of the time. (3)

4. Do you wake up during the night because of your asthma?
   - Yes, all of the time. (0)
   - Yes, most of the time. (1)
   - Yes, some of the time. (2)
   - No, none of the time. (3)

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?
   - Not at all (0)
   - 1-3 days (1)
   - 4-10 days (2)
   - 11-18 days (3)
   - 19-24 days (4)
   - Everyday (5)

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?
   - Not at all (0)
   - 1-3 days (1)
   - 4-10 days (2)
   - 11-18 days (3)
   - 19-24 days (4)
   - Everyday (5)

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?
   - Not at all (0)
   - 1-3 days (1)
   - 4-10 days (2)
   - 11-18 days (3)
   - 19-24 days (4)
   - Everyday (5)
Child-Asthma Control Test

- **Child**
  1. How is your asthma today?
  2. How much of a problem is your asthma when you run, exercise and play sports?
  3. Do you cough because of your asthma?
  4. Do you wake up during the night because of your asthma?

- **Parent**
  5. During the last 4 weeks how many days did your child have any daytime asthma symptoms?
  6. During the last 4 weeks how many days did your child wheeze during the day because of asthma?
  7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?
Validation of Asthma Control Test

Child-Asthma Control Test

- What does the Total score mean?
  - Severity, or
  - Confidence of assessment

- What use is the test?
  - Reminder
  - Progress
  - Pattern

- The profile is as important as the total score, e.g.
  - Exercise symptoms with no night or other symptoms
    - ? fixed obstruction or laryngeal dysfunction
  - Night symptoms with no exercise or other symptoms
    - ? Reflux associated airway disease
How would you manage Ben?

- Ben, 8, wakes with wheezing 3-4x/week, misses out on PE and refuses to take part in organised sport.
- He had 4 HDU stays for exacerbations in the last 6 months. Pre- and Post- FEV1 are 60% & 90% predicted.
- C-ACT score is 15
- He is currently taking fluticasone 125 µg ii bd. Compliance and spacer technique are excellent.

A. Increase daily fluticasone
B. Add LABA / ICS+LABA
C. Add montelukast
D. Change to SMART regime (prn Symbicort)
E. Add oral steroids
F. Other (radiology, ENT etc)
Goldilocks and the Three Stairs

82 children with uncontrolled asthma on fluticasone 100µg bd

assigned to all of these steps in random sequence

Fluticasone 250µg bd  Fluticasone 100µg bd  Fluticasone 100µg bd
+ LABA 50µg bd           + LTRA 5mg / 10 mg daily

ICS step-up  LABA step-up  LTRA step-up

Outcomes
prednisone use ↓180 mg , or else, asthma-control days ↓31 days or else FEV₁ ↑5%

A Pairwise Comparisons

- **LABA vs. ICS**
  - LABA better
  - Neutral
  - ICS better

- **LABA vs. LTRA**
  - LABA better
  - Neutral
  - LTRA better

- **ICS vs. LTRA**
  - ICS better
  - Neutral
  - LTRA better

Percent of Patients

Differential response

- Different response to the three different step-ups was observed in 98% of children
- Better LABA response predicted by
  - better Asthma Control scores ≥19
  - White & Hispanics
  - No eczema
- Better LTRA response predicted by
  - Older age >11 yr
  - Eczema
- BHR, FeNO, β-receptor genotype & season not predictive.

Adding montelukast vs LABA: Exercise challenge

How would you manage Ben?

Ben, 8, [still] wakes with wheezing 3-4x/week, misses out on PE and refuses to take part in organised sport.

He had 4 HDU stays for exacerbations in the last 6 months. Pre- and Post- FEV1 are 60% & 90% predicted.

He is currently taking fluticasone/salmeterol 125/25 µg ii bd and nasal steroids. Compliance and technique are excellent & CXR shows ↑AP but clear

A. Add extra daily fluticasone
B. Increase ICS/LABA combination
C. Change to SMART regime (prn Symbicort)
D. Add montelukast
E. Add oral steroids
F. Other
SMART therapy: Study design

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<th>Reliever</th>
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<td>Budesonide 320 µg o.d.</td>
<td>Terbutaline</td>
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<tr>
<td>Budesonide/formoterol 80/4.5 µg o.d.</td>
<td>Terbutaline</td>
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<tr>
<td>Budesonide/formoterol 80/4.5 µg o.d.</td>
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</table>

Sponsored by AstraZeneca
Symbicort vs terbutaline as reliever: all children on o.d. Symbicort 80/4.5 µg

Hospitalised exacerbations

Night wakings

Reliever use

Asthma control days

Symbicort 80/4.5 µg od as maintenance + reliever vs fixed dose budesonide 320 µg od

- Hospitalised exacerbations
- Night wakings
- Reliever use
- Height change

Time to severe exacerbations

Inhaled steroids and growth 2014

- ICS vs non-steroid or placebo
  - Growth velocity 0.48 cm/yr (0.30-0.65) lower
  - From baseline to 1 year shorter by 0.61 cm (0.38-0.83)
  - Children treated prepubertally: adult height 1.2 cm shorter
    - Kelly et al. NEJM 2012;367:904–12.

- 50-100 µg vs 200 µg beclomethasone equivalent
  - Difference of 0.2 cm (0.02-0.39) in first year
In infants with 2+ episodes of wheeze, family asthma and atopic eczema are fairly strong predictors of asthma at age 6–worth considering relievers, education and action plan. Bronchiolitis (except in the US) is not a default diagnosis for infant wheeze.

Infants with interval symptoms and atopy: modest improvement with inhaled steroids. Still room to be selective.

Preschool children with intermittent asthma: some evidence for pre-emptive high dose ICS. Variable evidence for regular montelukast.

Step-up therapy for chronic asthma: LABA > montelukast > increase, but substantial individual variation – try one then the other?

SMART regime – some gains. Selected cases (?poor compliance)

Inhaled steroids do not prevent remodelling or chronicity and probably do not alter the natural history of asthma. They do cause mild but consistent slowing of linear growth.

Mt Tasman & Mt Cook from Hokitika Beach
# Maintenance drug therapy of asthma in children

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<th>Efficacy</th>
<th>Safety</th>
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<td>Insufficient evidence</td>
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<td>McKean et al 2009</td>
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<td><strong>Control and Lung function better on regular</strong></td>
<td><strong>Growth better on intermittent</strong></td>
<td>Chauhan et al. 2013</td>
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<td>LABA vs doubling steroid</td>
<td>No difference in symptoms or episodes</td>
<td>Improved lung function and growth</td>
<td>Chroinin et al 2012</td>
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<td>Safety of LABA unclear</td>
<td>Cates et al 2012</td>
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<td>No adverse events</td>
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<td>Seddon et al 2009</td>
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<td><strong>Omalizumab (moderate asthma)</strong></td>
<td><strong>Less exacerbations, improved symptoms and QoL</strong></td>
<td><strong>Skin rashes</strong></td>
<td>Normansell et al 2014</td>
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<td>Macrolides</td>
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## Anti-allergen management

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<tr>
<td>House dust mite reduction</td>
<td>No evidence</td>
<td></td>
<td>Gøtzsche et al 2011</td>
</tr>
<tr>
<td>Pet allergen reduction</td>
<td>Insufficient evidence</td>
<td></td>
<td>Kilburn et al 2009</td>
</tr>
<tr>
<td>Feather bedding vs synthetic</td>
<td>No trials</td>
<td></td>
<td>Campbell et al 2009</td>
</tr>
</tbody>
</table>
## Non-drug treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational intervention</td>
<td><strong>Improves physiological measures in 6m and symptoms in 12m</strong></td>
<td></td>
<td>Wolf et al 208</td>
</tr>
<tr>
<td>Smartphone apps</td>
<td>Insufficient evidence</td>
<td></td>
<td>Belisario et al 2013</td>
</tr>
<tr>
<td>Family therapy</td>
<td><strong>Some evidence</strong></td>
<td></td>
<td>Yorke et al 2009</td>
</tr>
<tr>
<td>Swimming therapy</td>
<td><strong>Improves fitness and lung function but limited evidence re asthma control</strong></td>
<td></td>
<td>Beggs et al 2013</td>
</tr>
</tbody>
</table>
Treatment of nonspecific chronic cough with anti-asthma medication

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-agonists</td>
<td>No benefit</td>
<td></td>
<td>Tomerak et al 2009</td>
</tr>
<tr>
<td>ICS</td>
<td>No benefit</td>
<td></td>
<td>Tomerak et al 2009</td>
</tr>
<tr>
<td>Drug</td>
<td>Efficacy</td>
<td>Safety</td>
<td>Ref</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>IV salbutamol Vs inhaled bronchodilators</td>
<td>Insufficient evidence</td>
<td>Incr. tremors</td>
<td>Travis et al 2012</td>
</tr>
<tr>
<td>IV aminophylline Vs inhaled bronchodilators</td>
<td>Possible benefit in severe</td>
<td>Incr. vomiting</td>
<td>Mitra et al 2009</td>
</tr>
<tr>
<td>IV magnesium sulfate</td>
<td>Benefit in severe non-responding asthma in adults</td>
<td></td>
<td>Kew et al 2014</td>
</tr>
<tr>
<td>Heliox</td>
<td>Not supported as routine</td>
<td></td>
<td>Rodrigo et al 2010</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>Shorter stay, less readmission</td>
<td>Safe</td>
<td>Smith et al 2008</td>
</tr>
<tr>
<td>ICS vs oral steroids after ED</td>
<td>No benefit except in mild asthma</td>
<td></td>
<td>Edmonds et al 2012</td>
</tr>
<tr>
<td>Increasing maintenance ICS in acute asthma</td>
<td>No benefit</td>
<td>No AEs</td>
<td>Quon et al 2010</td>
</tr>
<tr>
<td>Early use of ICS vs placebo in ED</td>
<td>Some benefit over placebo</td>
<td>No AEs</td>
<td>Edmonds et al 2012</td>
</tr>
</tbody>
</table>
Clinical assessment of acute severity

- The barrier to airflow
  - mismatch between effort and air entry / chest expansion)

- Functional oximetry
  - Mental state
  - Ability to walk and talk

- Pulse oximetry