Montelukast, steroidi e wheezing infettivo ricorrente

A. Boner
Recurrent infectious wheezing: montelukast or corticosteroids?

**Introduction**
- When everything seemed to be clear
- A little bit of basic science
- When it seemed even more clear
- The renaissance of uncertainty
- Confusion again: no thank you
- A little bit of more basic science
- What we should probably do
- Conclusions

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✓ Birth cohort.
✓ Wheezing symptoms over first two years.
✓ Cognitive status of children at the age of 3 yr with the Bayley Mental Development Index (MDI).

Mental Development Index at age 3 yrs

<table>
<thead>
<tr>
<th>Category</th>
<th>MDI Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>104.3</td>
</tr>
<tr>
<td>Only in months 0-12</td>
<td>101.6</td>
</tr>
<tr>
<td>Persistent</td>
<td>97.5</td>
</tr>
</tbody>
</table>
Differential diagnosis of chronic or recurrent wheezing in infancy


Careful consideration of the pattern and nature of the symptoms including age at onset and variability of symptoms and signs is crucial before any treatment is undertaken. “Not all that wheeze is asthma”.

- Developmental anomalies
- Tracheo-oesophageal fistula and related disorders
- Bronchomalacia (localised or generalised)
- Stovepipe trachea
- Bronchial compression syndromes
- Vascular ring
- Anomalous origin of the right subclavian artery
- Bronchial or pericardial cyst
- Congenital heart disease (L–R shunting)
- Granuloma or polyps
- Host defence defect
- Cystic fibrosis
- Ciliary dyskinesia
- Defects of immunity

- Severe combined immune deficiency
- Combined IgA and IgG2 deficiency
- Postviral syndromes
- Recurrent viral infections
- Obliterative bronchiolitis
- Airway stricture or granuloma or lymphadenitis
- Recurrent aspiration
- Gastro-oesophageal reflux
- Disorders of swallowing
- Neuromuscular disease
- Mechanical disorders
- Perinatal disorders
- Chronic lung disease of prematurity
- Congenital infection
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From a sample of around 30,000 primary schoolchildren in Melbourne, 400 children were allotted to one of four groups, defined as follows:

1. **control group**: children who had never wheezed;
2. **"mild wheezy bronchitis" group**: children who had wheezed < 5 times, the wheezing always being associated with bronchitis, or apparent respiratory infection;
3. **"wheezy bronchitis" group**: children who had wheezed ≥ 5 times or more, the wheezing always being associated with bronchitis or apparent respiratory infection; and
4. **"asthma" group**: children who had wheezed, the wheezing being unassociated with symptoms of apparent respiratory infection on at least one occasion.

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4. **“asthma” group** - children who had wheezed, the wheezing being unassociated with symptoms of apparent respiratory infection on at least one occasion.

**Conclusions:**

1) wheezy bronchitis and asthma cannot be clearly distinguished,

2) patients belong to a single population with a genetically determined predisposition to disease that varies in severity and has differing precipitating factors.

3) the clinical management of these two groups is the same.

- Nearly half of the children had missed more than 6 weeks of school (or nursery) in the previous 12 months because of asthma, and 5 had missed more than three months.
- The word "asthma" was mentioned in the general practitioner's letter in only 6 out of 32 cases.
- The terms "wheezy bronchitis," "wheezing," or "bronchospasm" were used in 11 letters, but were not mentioned in a further 12, in which "recurrent chest infections," "recurrent cough," or "bronchitis" were given as diagnoses.

- 34 children with asthma (2-12 yrs old) referred to outpatient clinics in Newcastle upon Tyne (16 cases) and London (18 cases).

- **Hospital management:**
  All the parents were given an unequivocal diagnosis of asthma and an appropriate explanation.

- **Clinical response:**
  Most children showed appreciable clinical improvement. The most important single factor in this improvement seemed to be treatment with sodium cromoglycate.

✓ 34 children with asthma (2-12 yrs old) referred to outpatient clinics in Newcastle upon Tyne (16 cases) and London (18 cases)

Reluctance to use the word "asthma"

- This seems to be an important factor for undertreatment, and is understandable as inheritance from the '50s and '60s.

- During these years hospital paediatricians taught a whole generation of doctors to avoid using the word "asthma" when talking to parents, as it caused unnecessary upset by suggesting a crippling and potentially fatal disease.

✓ 34 children with asthma (2-12 yrs old) referred to outpatient clinics in Newcastle upon Tyne (16 cases) and London (18 cases)

- 179 Tyneside children seen by a doctor for chest wheezing symptoms,
- a diagnosis of asthma had been offered to the parents of only 21 children, including 3 of the 56 children experiencing 4 to 12 wheezy episodes a year and 11 of the 31 children experiencing more than 12 episodes a year.

<table>
<thead>
<tr>
<th>Diagnostic label</th>
<th>No in group*</th>
<th>Bronchodilator drugs:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-specific diagnoses</td>
<td>120</td>
<td>Regularly prescribed</td>
</tr>
<tr>
<td>Wheezy bronchitis or &quot;allergy&quot;</td>
<td>16</td>
<td>13%</td>
</tr>
<tr>
<td>Asthma</td>
<td>21</td>
<td>95%</td>
</tr>
</tbody>
</table>

*Parents of six children with non-specific chestiness and of two children with wheezy bronchitis or chest allergy did not know whether bronchodilators had ever been prescribed.

- 179 Tyneside children seen by a doctor for chest wheezing symptoms,
- a diagnosis of asthma had been offered to the parents of only 21 children, including 3 of the 56 children experiencing 4 to 12 wheezy episodes a year and 11 of the 31 children experiencing more than 12 episodes a year.

We found that over 96% of all children could be identified by the parents' reply to the single question, "Has your child ever had attacks of wheezing?"

Diagnosis presents a problem only when doctors fail to ask specifically about wheeze when parents volunteer less helpful symptoms such as cough or chestiness, as children are often free of overt wheeze by the time they are seen.
As a consequence pediatric pulmonologists suggested that all wheezing in infancy and early childhood should be labeled asthma. This resulted in more appropriate treatment with bronchodilators and antiinflammatory agents and in reduced morbidity.


but

also in "a loss of pathophysiological precision which may have implications that are not purely academic"

*Wilson NM, Arch Dis Child. 1989;64(8):1194-9*
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The Tucson Children's Respiratory Study (TCRS), begun in 1980, has followed 1246 subjects from birth together with their family members to delineate the complex interrelationships between a large number of potential risk factors, acute lower respiratory tract illnesses, and chronic lung disorders later in childhood and early adult life, especially asthma.

prevalence by age for the 3 different wheezing phenotypes
A CLINICAL INDEX TO DEFINE ASTHMA RISK

**Major CRITERIA**

1) Parental asthma
2) Atopic Dermatitis
3) Atopy

At least one

**Minor CRITERIA**

1) Allergic rhinitis
2) Wheezing apart from cold
3) Eosinophilia ($\geq 4\%$)

and/or

Two

If (-) 95% probability of not developing asthma

**If at least one major and/or minor criterion: early wheezing (< 3/year) 76% Risk of asthma development**

Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood J Henderson Thorax 2008;63;974

6265 children in a longitudinal birth cohort (the ALSPAC)
✓ from birth to 7 yrs
✓ phenotypes based on patterns of wheezing
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• Episodic treatment
The implication of these two studies, involving more than 900 children, is that any preschool child with viral induced wheeze who is well enough to stay in the community should not be prescribed oral prednisolone, and many children admitted to hospital also should not be prescribed oral prednisolone.

These studies, however, were undertaken in children with relatively mild symptoms and most were discharged from hospital in less than 24 hours, so what these studies do not tell us is whether prednisolone is indicated in really severe preschool viral wheeze.

Bush A, BMJ 2014; February 4
Preemptive use of high-dose fluticasone for virus-induced wheezing in young children.


- 129 non-atopic children (1-6 years)
- 750 μg fluticasone propionate or placebo twice daily, beginning at the onset of an upper respiratory tract infection and continuing for a maximum of 10 days, over a period of 6 to 12 months.

% children treated with one or more bursts of systemic corticosteroids

<table>
<thead>
<tr>
<th>Fluticasone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>39%</td>
<td>64%</td>
</tr>
<tr>
<td>RR=0.6</td>
<td>-0.36 cm</td>
</tr>
</tbody>
</table>

Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing.


- 12-month trial,
- 238 children (12 to 59 mo.)
- moderate-to-severe intermittent wheezing
- 7 days of either
  - BUD inhalation suspension (1 mg twice daily),
  - montelukast (4 mg daily), or
  - placebo in addition to albuterol with each identified respiratory tract illness.
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-37% for Mont $p=0.003$ vs pl
-38% for BUD $p=0.003$ vs pl
Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing.


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  - BUD inhalation suspension (1 mg twice daily),
  - montelukast (4 mg daily), or
  - placebo in addition to albuterol with each identified respiratory tract illness.

- 32% for Mont $p=0.01$ vs pl
- 40% for BUD $p=0.001$ vs pl
Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing.


“Regarding progression of the illness to the point of prednisolone use, it is possible that the initiation of high-dose budesonide or montelukast therapy after symptom onset and presumably after stimulation of the immune response usually triggered by an acute viral infection was incapable of changing the natural course of each such episode.”
Long-term preventive treatment

- Long-term preventive treatment is needed for persistent asthma.

Persistent Asthma: Daily Medication
- Consult with asthma specialist to ensure adherence to step 5.

Persistent Asthma: Daily Medication
- Consult with asthma specialist to ensure adherence to step 6.

Step 1: Preferred: Low-dose ICS
- Additional: Theophylline
- Alternative: Medium-dose ICS
- Alternative: N/A

Step 2: Preferred: Medium-dose ICS
- Alternative: Low-dose ICS + LABA
- Alternative: Medium-dose ICS + LABA

Step 3: Preferred: Medium-dose ICS
- alternative: Low-dose ICS + LABA, Theophylline, or Zafirlukast
- Alternative: Medium-dose ICS + LABA

Step 4: Preferred: Low-dose ICS + LABA
- Alternative: ICS + LABA

Step 5: Preferred: ICS + LABA, N/A
- Alternative: ICS + LABA

Step 6: Preferred: ICS + LABA, N/A
- Alternative: ICS + LABA

Quick-Relief Medication for All Patients
- As needed, short course of oral systemic corticosteroids may be needed.
- Lab test of sputum X days a week to help guide the need for step up in treatment.
Inhaled steroids for episodic viral wheeze of childhood.  

- 5 randomized controlled trials in children with a history of mild episodic viral wheeze
- Most of the children had previously required no or infrequent oral corticosteroids and had very infrequent hospital admissions.

**Relative Risk For Requirement of Oral Steroids**

<table>
<thead>
<tr>
<th>Description</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic high dose ICS (1.6-2.25 mg/day)</td>
<td>0.53</td>
</tr>
<tr>
<td>Maintenance low-dose ICS (400 µg/day)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

- 305 ch (12-47 mo.)
- Fluticasone 100 µg MDI x 2 with spacer vs placebo
- 4 week run-in
- 12 wks treatment

% increase in days without symptoms

<table>
<thead>
<tr>
<th></th>
<th>FP</th>
<th>Placebo</th>
<th>FP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>45%</td>
<td>25%</td>
<td></td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>p = 0.005</td>
<td></td>
<td>p = 0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

in ch with frequent symptoms (>3 days/wk) during run-in

in ch with a FH of asthma

ALB
Randomized controlled trial of fluticasone in preschool children with intermittent wheeze.


- Children 2-5 yrs
- FP 100 µg x2 for 6 wks or placebo
- Allergen sensitivity
- Airway resistance with interrupter technique ($R_{int}$)

Geometric mean change in resistance after 6 weeks of treatment with FP

SPT (+) ch

-5
-10
-15
-20

SPT (-) ch

0

$R_{int}$

$-16\%$

$p=0.1$

$p=0.003$

Compared to baseline

SPT (+) ch

$p=0.1$

-3.5

$p=0.003$

- 82 infants and young children during acute episodes of virus-induced wheezing vs
- 47 infants with uncomplicated upper respiratory infections

LTs were increased in wheezing subjects in comparison with those with upper respiratory infections ($p = 0.009$)

Concentrations of cysteinyl LTs in respiratory secretions
Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma.


- 549 (2-5 yrs) ch. with a history of episodic wheezing (PREVIA study);
- Montelukast 4-5 mg for 48 weeks; or placebo:
- Rates of exacerbations.

In montelukast treated group
% reduction in exacerbations/year

2.34 → 1.60
-32%

$p<0.001$
Percentage of patients with an exacerbation event

Placebo

Montelukast

Short-course montelukast for intermittent asthma in children: a randomized controlled trial.

Robertson CF, Am J Respir Crit Care Med. 2007;175(4):323-9

- 201 children (2-14 yrs) with intermittent asthma
- Short course of Montelukast (4 mg or 5 mg) introduced at the onset of an acute asthma episode and continued for a minimum of 7 days or until symptoms had resolved for 48 hours
- Follow-up 12 months

N° of acute episodes in 12 months study period

<table>
<thead>
<tr>
<th>Montelukast group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>345</td>
<td>335</td>
</tr>
</tbody>
</table>

![Chart showing comparison between Montelukast group and Placebo group]
Short-course montelukast for intermittent asthma in children: a randomized controlled trial.
Robertson CF, Am J Respir Crit Care Med. 2007;175(4):323-9

In Montelukast treated group compared to placebo

- Emergency department visits: -46.6% (p<0.05)
- Overall acute health care utilization: -23.6% (p<0.01)
- Nights awakened per episode: -9.4%
- Time off school: -36.6% (p<0.0001)
- Time off works for parents: -33.5% (p<0.0001)
Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy.


- 194 asthmatic children
- 2 to 14 years
- Montelukast or placebo in addition to usual asthma therapy between September 1 and October 15, 2005.

![Bar graph showing % days with worse asthma symptoms]

- Placebo: 8.3% (p<0.02)
- Montelukast: 3.9%

### TABLE 1
Definitions used in the present report

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Temporal pattern of wheeze</strong></td>
<td></td>
</tr>
<tr>
<td>Episodic (viral) wheeze</td>
<td>Wheezing during discrete time periods, often in association with clinical evidence of a viral cold, with absence of wheeze between episodes.</td>
</tr>
<tr>
<td>Multiple-trigger wheeze</td>
<td>Wheezing that shows discrete exacerbations, but also symptoms between episodes.</td>
</tr>
<tr>
<td><strong>Duration of wheeze</strong></td>
<td></td>
</tr>
<tr>
<td>Transient wheeze</td>
<td>Symptoms that commenced before the age of 3 yrs and are found (retrospectively) to have disappeared by the age of 6 yrs; transient wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Persistent wheeze</td>
<td>Symptoms that are found (retrospectively) to have continued until the age of ≥6 yrs; persistent wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
<tr>
<td>Late-onset wheeze</td>
<td>Symptoms that start after the age of 3 yrs; late-onset wheeze may be episodic or multiple-trigger wheeze</td>
</tr>
</tbody>
</table>

1) Based on the limited evidence available, inhaled short-acting β2-agonists by metered-dose inhaler/spacer combination are recommended for symptomatic relief.

2) Educating parents regarding causative factors and treatment is useful. Exposure to tobacco smoke should be avoided; allergen avoidance may be considered when sensitisation has been established.

3) Maintenance treatment with inhaled corticosteroids is recommended for multiple-trigger wheeze; benefits are often small.

4) Montelukast is recommended for the treatment of episodic (viral) wheeze and can be started when symptoms of a viral cold develop.
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Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis.


Pooled RRs for wheezing/asthma exacerbations (with 95% CIs) of eligible studies comparing ICSs with placebo favors ICS.

- 29 randomized, prospective, controlled trials published January 1996 to March 2008 with a minimum of 4 weeks of inhaled corticosteroids versus placebo
- (N = 3592 subjects < 5 years old)

\[ RR = 0.59, \quad P < 0.0001 \] in favor of ICS
Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis.


- 29 randomized, prospective, controlled trials published January 1996 to March 2008 with a minimum of 4 weeks of inhaled corticosteroids versus placebo
- (N = 3592 subjects < 5 years old)

RR of wheezing/asthma Exacerbations with ICS

\[ \text{RR} = 0.65 \]

\[ P = 0.04 \]
Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis.


Posthoc subgroup analysis suggests that this effect was:

1) higher in those with a diagnosis of asthma than wheeze but

2) was independent of:
   - age (infants versus preschoolers),
   - atopic condition,
   - type of inhaled corticosteroid (budesonide MDI versus fluticasone MDI),
   - mode of delivery (MDI versus nebulizer),
   - study quality (Jadad score: <4 vs ≥ 4)
   - study duration (<12 vs ≥ 12 weeks).
The effect of montelukast on respiratory symptoms and lung function in wheezy infants

Pelkonen, ERJ 2013; 41: 664-670

113 (6-24-mo-old-children) with recurrent wheezing.

Placebo or montelukast daily for an 8-week period.

Symptom-free days, rescue medication, lung function (squeeze technique), airway responsiveness (dosimetric methacholine challenge test), FeNO.

Weeky symptoms-free days

- Montelukast: 3.1
- Placebo: 2.7

ns
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Effectiveness of Nebulized Beclomethasone in Preventing Viral Wheezing: An RCT
Clavenna A. Pediatrics, 2014;133:e505-12

✓ 521 children aged 1 to 5 yrs with at least 1 episode of viral wheezing in the last 12 months, presenting to any of 40 Italian pediatricians for an upper respiratory tract infection.

✓ Randomly allocated to receive beclomethasone 400 mg or placebo twice daily for 10 days. Medications were administered through a nebulizer.

% children with diagnosed wheezing

9.0%
Effectiveness of Nebulized Beclomethasone in Preventing Viral Wheezing: An RCT

Clavenna A. Pediatrics, 2014;133:e505-12

Day-by-day overall asthma-like symptom score (mean and 95% CI)
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Isolation of cells from the lower airways in infants with wheeze by sputum induction

Gaillard, Eur Respir J 2013;41:483

6 wheezing infants with age range 6-14 months (3 infants with eczema and + FH)

Median percentage of

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Median Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial cells</td>
<td>32%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0%</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>56%</td>
</tr>
<tr>
<td>Macrophages</td>
<td>44%</td>
</tr>
</tbody>
</table>

✓ RBM thickness and numbers of inflammatory cells in endobronchial biopsies from 53 infants during clinical bronchoscopy for severe wheeze and/or cough:

- **Group A**: 16 infants (median age 12 mo) with decreased specific airway conductance (sGaw) and bronchodilator reversibility;
- **Group B**: 22 infants (median age of 12.4 mo) with decreased sGaw without bronchodilator reversibility;
- **Group C**: 15 infants (median age of 11.5 mo) with normal sGaw.

✓ In addition:

- **Group D**: 17 children, (median age 10.3 yrs) with difficult asthma;
- **Group E**: 10 control children without asthma,
- **Group F**: 9 healthy adults
Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction.

*Saglani S, Am J Respir Crit Care Med 2005;171:722-7*

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  - **Group A**: 16 infants (median age 12 mo) with decreased specific airway conductance \( sGaw \) and bronchodilator reversibility;
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- In addition:
  - **Group D**: 17 children, (median age 10.3 yrs) with difficult asthma;
  - **Group E**: 10 control children without asthma,
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RBM thickness in all infants with atopy compared with infants without atopy.
Sputum inflammatory phenotypes are not stable in children with asthma

L Fleming, Thorax 2012;67:675

- 51 children with severe & 28 with mild to moderate asthma;
- Samples classified as: eosinophilic (>2.5% E), neutrophilic (>54% N), mixed granulocytic (>2.5% E, >54% N), paucigranulocytic (<2.5% E, <54% N);
- Sputum induction repeated every 3 mo. over a 1-yr period.

% children that in the longitudinal analysis demonstrated ≥2 phenotypes

63%
Sputum inflammatory phenotypes are not stable in children with asthma

*L Fleming, Thorax 2012;67:675*

Changes in sputum eosinophils (A) and neutrophils (B) over the duration of the study in the severe asthma group.

The dotted line denotes the 2.5% cut-off point for sputum eosinophils and the 54% cut-off point for neutrophils.
Sputum inflammatory phenotypes are not stable in children with asthma

*L Fleming, Thorax 2012;67:675*

Changes in sputum **eosinophils (A)** and **neutrophils (B)** over the duration of the study in the **mild to moderate** asthma group.

The dotted line denotes the 2.5% cut-off point for sputum eosinophils and the 54% cut-off point for neutrophils.
Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

Nwokoro C, Lancet Respir Med 2014;2:796


21 primary care sites and 41 secondary care sites in England and Scotland.

Children aged 10 months to 5 years with ≥ 2 wheeze episodes were allocated to either a 5/5 or 5/x+x/x ALOX5 promoter genotype stratum, then randomly assigned (1:1) to intermittent montelukast (n=669) or placebo (n=677) given by parents at each wheeze episode over a 12 month period.

Mean unscheduled medical attendances for wheezing episodes:

- Montelukast: 2.0
- Placebo: 2.3

\( p = 0.06 \)
Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

Nwokoro C, Lancet Respir Med 2014;2:796

- 21 primary care sites and 41 secondary care sites in England and Scotland.
- Children aged 10 months to 5 years with ≥ 2 wheeze episodes were allocated to either a 5/5 or 5/x+x/x ALOX5 promoter genotype stratum, then randomly assigned (1:1) to intermittent montelukast (n=669) or placebo (n=677) given by parents at each wheeze episode over a 12 month period.

Mean unscheduled medical attendances for wheezing episodes of the children are in the 5/5 stratum for arachidonate 5-lipoxygenase in children (62.5%)

![Graph showing mean unscheduled medical attendances for wheezing episodes of children with intermittent montelukast or placebo. The graph indicates a significant difference between the two groups, with p = 0.01. The x-axis represents Montelukast and Placebo, and the y-axis represents the number of attendance episodes. The montelukast group has a mean of 2.0 attendances, while the placebo group has a mean of 2.4 attendances.]
Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial

Nwokoro C, Lancet Respir Med 2014;2:796

Mean unscheduled medical attendances for wheezing episodes of the children are in the 5/5 stratum for arachidonate 5-lipoxygenase in children (62.5%)

62.5% of the children are in the 5/5 stratum which may identify a montelukast responsive group.

In black children this allele is less frequent (31%)


21 primary care sites and 41 secondary care sites in England and Scotland.

Children aged 10 months to 5 years with ≥ 2 wheeze episodes were allocated to either a 5/5 or 5/x+x ALOX5 promoter genotype stratum, then randomly assigned (1:1) to intermittent montelukast (n=669) or placebo (n=677) given by parents at each wheeze episode over a 12 month period.

Montelukast

Placebo

2.0

2.4

$p = 0.01$
Hair Zinc and Selenium Levels in Children With Recurrent Wheezing

✓ Zn and Se levels
✓ 65 patients with recurrent wheezing (RW) and 65 healthy children (HC)
✓ Total antioxidant capacity (TAC) (mmol/L)

Hair levels (μg/g)

<table>
<thead>
<tr>
<th></th>
<th>Zn</th>
<th>Se</th>
</tr>
</thead>
<tbody>
<tr>
<td>RW</td>
<td>162</td>
<td>217</td>
</tr>
<tr>
<td>HC</td>
<td>236</td>
<td>280</td>
</tr>
</tbody>
</table>

P<0.001
Hair Zinc and Selenium Levels in Children With Recurrent Wheezing


- Zn and Se levels
- 65 patients with recurrent wheezing (RW) and 65 healthy children (HC)
- Total antioxidant capacity (TAC) (mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>RW</th>
<th>HC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>1.6–1.5</td>
<td>1.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1.4–1.3</td>
<td>1.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2–1.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0–0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recurrent infectious wheezing: montelukast or corticosteroids?

✓ Introduction
✓ When everything seemed to be clear
✓ A little bit of basic science
✓ When it seemed even more clear
✓ The renaissance of uncertainty
✓ Confusion again: no thank you
✓ A little bit of more basic science
✓ What we should probably do
✓ Conclusions
1) The distinction between EVW and MTW is not clear in all patients.

2) Some children retain a consistent pattern of EVW or MTW, but symptom patterns change over time in many patients and their airway pathology remains unclear.

3) Severity and frequency of episodes seem to be at least as important to distinguish between children as the distinction between EVW and MTW.
1) In children with MTW, ICS are the first choice for daily controller therapy.

2) In children with EVW, daily therapy may be considered with either ICS or montelukast if:

- the attacks are severe (requiring hospital admission or systemic corticosteroids); or
- the attacks are frequent (≥ episodes in a season); or
- the clinician suspects that interval symptoms are being under reported.
3) Any controller therapy should be viewed as a treatment trial for 6-8 weeks, with scheduled follow-up.

4) Discontinue treatment if there has been no benefit, and consider also alternative diagnoses (GINA guidelines August 2014).

5) Take favourable natural history into account: taper down to lowest effective dose, and discontinue treatment if the child has been symptom-free for 3 months on low-dose therapy.
1) **Oral corticosteroids are not indicated** in preschool children with an exacerbation of viral wheeze who do not need to be admitted to hospital.

2) **Oral corticosteroids are indicated only in preschool children admitted to hospital with very severe wheeze**; even in this group, evidence to support the use of prednisolone is not robust.

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**2013 consensus statement on classification and management of preschool wheezing disorders**

*Brandt PLP, Eur Respir J 2014;43:1172*
Stepwise approach – pharmacotherapy (children ≤5 years)

**PREFERRED CONTROLLER CHOICE**

**STEP 1**
- Daily low dose ICS
- Leukotriene receptor antagonist (LTRA)
- Intermittent ICS

**STEP 2**
- As-needed short-acting beta₂-agonist (all children)

**STEP 3**
- Double ‘low dose’ ICS
- Low dose ICS + LTRA
- Add LTRA Inc. ICS frequency
- Add intermittent ICS

**STEP 4**
- Continue controller & refer for specialist assessment

**CONSIDER THIS STEP FOR CHILDREN WITH:**

- **Infrequent viral wheezing and no or few interval symptoms**
  - Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year
  - Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months.

- **Asthma diagnosis, and not well-controlled on low dose ICS**
  - First check diagnosis, inhaler skills, adherence, exposures

- **Not well-controlled on double ICS**
‘Low dose’ inhaled corticosteroids (mcg/day) for children ≤5 years

<table>
<thead>
<tr>
<th>Inhaled corticosteroid</th>
<th>Low daily dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclometasone dipropionate (HFA)</td>
<td>100</td>
</tr>
<tr>
<td>Budesonide (pMDI + spacer)</td>
<td>200</td>
</tr>
<tr>
<td>Budesonide (nebulizer)</td>
<td>500</td>
</tr>
<tr>
<td>Fluticasone propionate (HFA)</td>
<td>100</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>160</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Not studied below age 4 years</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>Not studied in this age group</td>
</tr>
</tbody>
</table>

- This is not a table of equivalence
- A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety
## Choosing an inhaler device for children ≤5 years

<table>
<thead>
<tr>
<th>Age</th>
<th>Preferred device</th>
<th>Alternate device</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 years</td>
<td>Pressurized metered dose inhaler plus dedicated spacer with face mask</td>
<td>Nebulizer with face mask</td>
</tr>
<tr>
<td>4–5 years</td>
<td>Pressurized metered dose inhaler plus dedicated spacer with mouthpiece</td>
<td>Pressurized metered dose inhaler plus dedicated spacer with face mask, or nebulizer with mouthpiece or face mask</td>
</tr>
</tbody>
</table>
Future research

Antioxidants?

FUTURE directions

the next 5 years

- 41 children (mean age 31.9 ± 17.4 months, range 1-6 years) with wheezing to the emergency department
- randomized after 1 albuterol inhalation to receive either 4 mL of hypertonic saline 5% (HS) (n = 16) or 4 mL of normal saline (NS) (n = 25),
- both with 0.5 mL albuterol, twice every 20 minutes in the emergency department and 4 times a day thereafter if hospitalized.

The LOS was shorter in the HS than in the NS group: median 2 days versus 3 days (P = 0.027).
41 children (mean age 31.9 ± 17.4 months, range 1-6 years) with wheezing to the emergency department randomized after 1 albuterol inhalation to receive either 4 mL of hypertonic saline 5% (HS) (n = 16) or 4 mL of normal saline (NS) (n = 25), both with 0.5 mL albuterol, twice every 20 minutes in the emergency department and 4 times a day thereafter if hospitalized.

<table>
<thead>
<tr>
<th>admission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonic saline</td>
</tr>
<tr>
<td>normal saline</td>
</tr>
</tbody>
</table>

$p=0.027$
Recurrent infectious wheezing: montelukast or corticosteroids?

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- What we should probably do
- Conclusions
The group agreed that the decision to start maintenance treatment is primarily determined by the severity and frequency of wheeze episodes.

- There was consensus that ICS are the first-choice maintenance therapy for MTW.

- In Episodic Viral Wheeze, either ICS or montelukast may be prescribed.

- Any treatment given should be viewed as a therapeutic trial; regular scheduled follow-up is essential to review the response to treatment.

- If there is no benefit of the controller therapy started after 2-3 months, it should be discontinued and the child investigated further for alternative diagnosis.

- If symptoms resolve during controller therapy, this may be due either to an effect of treatment or to the favourable natural history of preschool wheezing. This can only be distinguished by withdrawing treatment after the child has become symptom free and to restart treatment only if symptoms recur.
The group agreed that the decision to start maintenance treatment is primarily determined by the severity and frequency of wheeze episodes. This can only be distinguished by weaning treatment after the child has become symptom free and to restart treatment only if symptoms recur.

The goals of asthma management are achieved through a partnership between the patient/carer and the health professional team, with a cycle of:

- **Assess** (diagnosis, symptom control, risk factors, inhaler technique adherence, parent preference)
- **Adjust treatment** (medications, non-pharmacological strategies, and treatment of modifiable risk factors)
- **Review response** including medication effectiveness and side effects
Grazie per la vostra attenzione

FORMAT  23-24/04/ 2015 Verona
Grazie per la vostra attenzione alla storia che vi ha raccontato mio nonno.