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Why Don’t Pharmacological Agents Work Well in Treatment of Asthma in Young Children

Diagnosis of asthma/wheezing in young children is not easy

- Recurrent wheezing occurs in a large proportion of children 5 years and younger, typically with viral upper respiratory tract infections. Deciding when this is the initial presentation of asthma is difficult.
- Previous classifications of wheezing phenotypes (episodic wheeze and multiple-trigger wheeze; or transient wheeze, persistent wheeze and late-onset wheezing) is more likely if they have:
  - Wheezing or coughing that occurs with exercise, laughing or crying in the absence of an apparent respiratory infection
  - A history of other allergic disease (eczema or allergic rhinitis) or asthma in first-degree relatives
  - Clinical improvements during 2-3 months of controller treatment, and worsening after cessation.

Drug Low daily dose ($\mu g$)

- Beclomethasone dipropionate (HFA) 100
- Budesonide pMDI + spacer 200
- Budesonide nebulized 500
- Fluticasone propionate (HFA) 100
- Ciclesonide 160
- Momenasone furoate Not studied below age 4
- Triamcinolone acetate Not studied


Clinical Questions

1. Does asthma medication prevent recurrent wheeze after RSV infection?
2. Does asthma medication prevent the development of asthma after RSV infection?
3. Is asthma medication effective for preschool children with recurrent wheeze?
4. Is intermittent asthma medication effective for recurrent wheeze/asthma?
CQ1: Does asthma medication prevent recurrent wheeze after RSV infection?

Background

- RSV bronchiolitis may be causally related to recurrent wheeze in early life in late preterm infants.

![Graph showing effect of ICS on recurrent wheeze](Image)


CQ1-1: Does ICS prevent recurrent wheeze after RSV infection?

**Patients:** 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

**Interventions:** 200 μg BDP (HFA) twice daily or matched placebo administered by a pressurised metered dose inhaler and a spacer during the first 3 months after hospital admission.

**Primary outcome:** the number of days with wheeze in the year after the three month intervention period.


CQ1: Does asthma medication prevent recurrent wheeze after RSV infection?

- Leukotriene receptor antagonist (LTRA)

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?


Efficacy results during the 4-week (period I) and 24-week (periods I+II) treatment periods


Patients: 200 infants (age, 6-24 months) hospitalized with their first episode of acute RSV bronchiolitis

Interventions: montelukast or placebo for 3 months (12 weeks)

Primary outcome: effect of montelukast on eosinophil degranulation in RSV bronchiolitis by measuring EDN levels.

Secondary outcome: recurrent wheezing episodes

Post-hoc analysis

- Percentage of symptom-free days over Week 2
- ≤30% (less severe)
- ≥30% (more severe)
CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

Symptom scores during the first 100 days after inclusion (14 weeks)


Number of exacerbations:
- Montelukast 41 (median of 1 per patient [quartiles 0–3] )
- Placebo 54 (median of 2 per patient [quartiles 0–3] (p = 0.57)

During the 1 year follow-up
- Median time [quartiles] interval to the first exacerbation:
  - Montelukast 25 days [0–77]
  - Placebo 6 days [0–58] for (p = 0.17)

CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?


EDA
Incidence of post-bronchiolitis recurrent wheezing
- Montelukast may reduce the frequency of post-bronchiolitic wheezing without causing significant side effects but that it has no effects on decreasing incidences of recurrent wheezing, symptom-free days, or the associated usage of corticosteroid in post-bronchiolitis patients.
- The small number of enrolled participants and the inability to pool all clinical outcomes precludes us from making solid recommendations.
- Subgroups that respond well to montelukast may exist.


CQ1-2: Does montelukast prevent recurrent wheeze after RSV infection?

• Leukotriene inhibitors may not be effective for acute symptoms of bronchiolitis

Leukotriene inhibitors may not be effective for acute symptoms of bronchiolitis

Length of hospital stay.

Clinical severity score (day 2)

The current evidence does not allow definitive conclusions to be made about the effects of leukotriene inhibitors on length of hospital stay and clinical severity score in infants and young children with bronchiolitis.

CQ2: Does asthma medication prevent the development of asthma after RSV infection?

Background
- Associations between viral bronchiolitis and the development of asthma during childhood and adolescence


CQ2: Does asthma medication prevent the development of asthma after RSV infection?

- ICS

CQ2-1: Does ICS prevent the development of asthma after RSV infection?

Patients: 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

Interventions: 200 μg BDP (HFA) twice daily or matched placebo administered by a pressurised metered dose inhaler and a spacer during the first 3 months after hospital admission.

Primary outcome: lung function, proportion of atopic diseases and height at 6 years of age.


No difference

CQ2-1: Does ICS prevent the development of asthma after RSV infection?

Patients: 243 previously healthy infants (126 boys, 117 girls) aged less than 13 months and admitted to hospital with respiratory syncytial virus infection.

Interventions: 200 μg BDP (HFA) twice daily or matched placebo administered by a pressurised metered dose inhaler and a spacer during the first 3 months after hospital admission.

Primary outcome: lung function, proportion of atopic diseases and height at 6 years of age.


Early initiated prolonged treatment with high-dose inhaled beclomethasone during hospitalization for respiratory syncytial virus infection during infancy did not improve the long-term respiratory outcome, but was safe.

CQ2: Does asthma medication prevent the development of asthma after RSV infection?

- Leukotriene receptor antagonist (LTRA)

No study has been reported

CQ3: Is asthma medication effective for preschool children with recurrent wheeze?

- ICS
CQ3-1: Is ICS effective for preschool children with recurrent wheeze?

**A Systematic Review**

Inclusion criteria for trials

1. Infants (1–23 months old) or preschoolers (2–5 years old) with a clinical diagnosis of wheezing or asthma for at least 6 months before study entry;
2. Randomized (parallel group or crossover) controlled trials;
3. A minimum of 4 weeks of treatment with ICSs (delivered via metered-dose inhaler [MDI] or nebulizer) compared with placebo;
4. Primary outcome measure of wheezing/asthma exacerbations (WAEs), define as worsening symptoms that required systemic corticosteroid use.


CQ3: Is asthma medication effective for preschool children with recurrent wheeze?

- Leukotriene inhibitors

CQ3-2: Is montelukast effective for preschool children with recurrent wheeze?

**Patients:** 549 children aged 2 to 5 years with a history of intermittent asthma symptoms.

**Interventions:** montelukast (n=278) or placebo (n=271) once per day for 12 months.

**Primary outcome:** the number of asthma exacerbation episodes defined as any three consecutive days with daytime symptoms (average score of four daily daytime symptom questions of at least 1.0 on each day) and at least two treatments of beta-agonist per day, or rescue use of oral/inhaled corticosteroids during 1 or more days, or a hospitalization because of asthma.


Montelukast effectively reduced asthma exacerbations in 2- to 5-year-old patients with intermittent asthma over 12 months of treatment and was generally well tolerated.

**Montelukast**

![Montelukast graph]

**Placebo**

![Placebo graph]
CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- ICS
- Leukotriene receptor antagonist (LTRA)

CQ4-1: Is intermittent asthma medication effective for recurrent wheeze/asthma?

Patients: 238 children aged 12 to 59 months with moderate-to-severe intermittent wheezing.

Interventions: 7 days of either budesonide inhalation suspension (1 mg twice daily), montelukast, or placebo in addition to albuterol with each identified respiratory tract illness (RTI) during the 12-month trial

Primary outcome: Proportion of episode-free days (EFDs)


Budesonide or montelukast initiated at early signs of RTI significantly reduced episode severity relative to conventional therapy. Montelukast reduced... wheezing trouble breathing activity limitation. Budesonide reduced... trouble breathing activity limitation.

CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- Leukotriene receptor antagonist (LTRA)

CQ4-2: Is intermittent montelukast effective for recurrent wheeze/asthma?

- Leukotriene receptor antagonist (LTRA)

Patients: >1358 Children aged 10 months to 5 years with two or more wheeze episodes initiated intermittent montelukast or placebo given by parents at each wheeze episode over a 12 month period. allocated to either a 5/5 or 5/x+x/x ALOX5 promoter genotype stratum.

Primary outcome: number of unscheduled medical attendances for wheezing episodes.


Treatment response in the primary analysis, and by 5/5 and 5/x + x/x strata.


No clear benefit of intermittent montelukast in young children with wheeze. However, the 5/5 ALOX5 promoter genotype might identify a montelukast-responsive subgroup.

CQ4: Is intermittent asthma medication effective for recurrent wheeze/asthma?

- ICS; intermittent versus daily
**CQ4-3: Is intermittent ICS effective for recurrent wheeze/asthma?**

**Patients:** 278 children between the ages of 12 and 53 months who had positive values on the modified API, recurrent wheezing episodes, and at least one exacerbation in the previous year but a low degree of impairment.

**Interventions:** randomly assigned to receive a budesonide inhalation suspension for 1 year as either an intermittent high-dose regimen (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness) or a daily low-dose regimen (0.5 mg nightly) with corresponding placebos.

**Primary outcome:** frequency of exacerbations requiring oral glucocorticoid therapy.

<table>
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<th>Characteristic</th>
<th>Total</th>
<th>Intermittent Regimen</th>
<th>Daily Regimen</th>
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<tr>
<td>Head circumference (cm)</td>
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</table>

**Summary**

- **Diagnosis** is the key...
  - whether a young child with recurrent wheeze needs asthma controllers?
- **Prevention**
  - Post-RSV: Montelukast may be effective?, not ICS
- **Long-term control**
  - ICS is the mainstay, montelukast is also effective
  - Intermittent use...still to be studied
  - Genotype or endotype-specific treatment?