THE WHEEZY CHILD - WHAT IS THE EVIDENCE FOR STEROIDS?

Dr Tim McDonald

09/11/2019   National Museum of Australia
Is Orange The New Black?
Is Orange The New Black?
“In what time does the peculiarity of the asthmatic exist?

Manifestly it is a morbid proclivity of the musculonervous system of his bronchial tubes to be thrown into a state of activity.

There is no peculiarity in the stimulus, the air breathed is the same to the asthmatic as the non-asthmatic.

It is clear that the vice in asthma consists, not in the production of any special irritant but in the irritability of the part irritated.”

Slater 1860
Definition Of Childhood Asthma

• “intermittent symptoms of wheeze, breathlessness and cough, with variable airflow obstruction documented in cooperative children, changing spontaneously over time and with treatment”.

• This covers episodic viral wheeze and multiple trigger wheeze in pre-school children, and atopic asthma in school age children.”

A.Bush; Ped Resp Rev 2013

• “Recurrent, Reversible, Small airways narrowing”

McDonald 1998
For safety, GINA no longer recommends treatment with short-acting beta2-agonists (SABA) alone. There is strong evidence that SABA-only treatment, although providing short-term relief of asthma symptoms, does not protect patients from severe exacerbations, and that regular or frequent use of SABAs increases the risk of exacerbations.

GINA now recommends that all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily low dose ICS-containing controller treatment, to reduce their risk of serious exacerbations.

For pre-school asthma, additional suggestions are provided for investigating a history of wheezing episodes (p.133). In pre-school children, recent studies suggest that clinical and/or inflammatory features may predict better short-term response to ICS, but more studies are needed (p.139). Early referral is recommended if the child fails to respond to controller treatment.

For exacerbations in pre-school children, OCS are not generally recommended except in emergency department and hospital settings (p.147). Follow-up after ED or hospital admission is recommended within 1-2 working days, and again 3-4 weeks later (p.152).

For all ages, the importance of confirming the diagnosis of asthma at initial presentation is emphasized, with new data finding that the diagnosis cannot be confirmed in around 30% of people with asthma in the community.
Box 7. The GINA asthma treatment strategy

Adults & adolescents 12+ years

Personalized asthma management:
Assess, Adjust, Review response

Symptoms
Exacerbations
Side-effects
Lung function
Patient satisfaction

Asthma medication options:
Adjust treatment up and down for individual patient needs

PREFERRED CONTROLLER
to prevent exacerbations and control symptoms

Other controller options

PREFERRED RELIEVER
Other reliever option

As-needed low dose ICS-formoterol *

Low dose ICS taken whenever SABA is taken†

Leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken†

As-needed short-acting β2-agonist (SABA)

For children 6–11 years, the preferred Step 3 treatment is low dose ICS-LABA or medium dose ICS.
Why we have the youngest customers in the business

This young person is 12 months old—and he isn't our youngest customer by many miles.

Put 7-Up in a glass or whelk, or serve it to babies and feel good about it. Look at the back of a 7-Up bottle. Notice that all our ingredients are listed. That isn't required of soft drinks, you know—but we're proud to do it and we think you'd be pleased that we do.

By the way, Mom, when it comes to toddlers—if they like to be counted to book them milk, try this: Add 7-Up to the milk in equal parts, pour the 7-Up gently into the milk. It's a wholesome combination—and it works! Make 7-Up your family drink. You like it...if this you?

Nothing does it like Seven-Up!
Bronchiolitis is a viral induced infection of the lower airways. However, there is no consensus on the age range, (1yr, <2yrs, or older) \[10\]. Disagreement about the important physical examination findings \[1, 2\].

- North American definition emphasizes wheeze as the hallmark physical finding \[11\] and bronchiolitis would not be diagnosed in the absence of wheeze.

- U.K. model \[2\] places more emphasis on crackles with the recognition that many patients will have wheeze as well. However, bronchiolitis could be diagnosed in the absence of wheeze.

Another area of disagreement among guidelines is whether bronchiolitis can only be diagnosed with the first episode of typical presentation versus repeated episodes.

“…. the heterogeneity in bronchiolitis definitions directly translates into a non-coherent collection of endotypes being incorrectly grouped under the term bronchiolitis ….” \[10\]

Improving Evidence Based Bronchiolitis Care

Amie A. Cahill, Joanna Cohen

Bronchiolitis is the number one cause of hospitalization in infants during the first 12 months of life resulting in approximately 100,000 hospital admissions annually.1,2 In the United States this translates to an estimated cost of $1.73 billion and direct medical costs exceeding $500 million.2 Clinical guidelines recommend primarily supportive care and discourage the use of pharmacotherapies and diagnostics as they do not improve outcomes.3-9 However, there continues to be wide variability in hospital-based care for bronchiolitis both among US and international institutions.2,10,11 Given the high financial and medical burden of bronchiolitis on families and healthcare facilities, it is prudent to continue reviewing evidence based management of this common disease in order to optimize resource utilization, decrease healthcare costs, and decrease unnecessary hospitalization.11,12
**Medication**

- Beta 2 agonists — Do not administer beta 2 agonists (including those with a personal or family history of atopy)
- Corticosteroids — Do not administer systemic or local glucocorticoids (nebulised, oral, intramuscular (IM) or IV)
- Adrenaline — Do not administer adrenaline (nebulised, IM or IV) except in peri-arrest or arrest situation
- Hypertonic Saline — Do not administer nebulised hypertonic saline
- Antibiotics — Including Azithromycin are not indicated in bronchiolitis
- Antivirals — Are not indicated

**Nasal suction**

- Nasal suction is not routinely recommended. Superficial nasal suction may be considered in those with moderate disease to assist feeding
- Nasal saline drops may be considered at time of feeding

**Chest physiotherapy**

- Is not indicated

**ONGOING MANAGEMENT**

- HFNC or Nasal CPAP therapy may be considered in the appropriate ward setting
The primary outcome was episodes requiring oral corticosteroids. Secondary outcomes addressed episode severity, frequency and duration and parental treatment preference.

Five randomised controlled trials in children with a history of mild episodic viral wheeze were identified.

Most of the children had previously required no or infrequent oral corticosteroids and had very infrequent hospital admissions.

3 studies of preschool children given episodic high dose ICS - (1.6 - 2.25 mg per day)

2 studies of maintenance ICS (400 micrograms per day), 1 of PSW, & 1 of children aged 7 -9 years.

High dose ICS showed decreased need oral corticosteroids (Relative risk (RR)=0.53, 95% CI: 0.27, 1.04).

This review of trials found high dose inhaled corticosteroids help treat mild episodic viral wheeze of childhood.

There is no evidence to support the use of maintenance low dose inhaled corticosteroids to prevent or manage episodic mild wheeze caused by a virus.

More research is needed.
RCTs comparing short-term systemic or inhaled glucocorticoids versus placebo or another intervention in children under 24 months with acute bronchiolitis (first episode with wheezing).

Our primary outcomes were: admissions by days 1 and 7 for outpatient studies; and length of stay (LOS) for inpatient studies.

Secondary outcomes included clinical severity parameters, healthcare use, pulmonary function, symptoms, quality of life and harms.

17 trials (2596 participants);

Glucocorticoids did not significantly reduce outpatient admissions by days 1 and 7 cf placebo

There was no benefit in LOS for inpatients (mean difference -0.18 days; 95% CI -0.39 to 0.04).

Further research is needed
Six trials involving 321 infants in three different settings were included. Compared with beta2-agonist alone, the combination of ipratropium bromide and beta2-agonist was associated with a reduced need for additional treatment, but no difference was seen in treatment response, respiratory rate or oxygen saturation improvement in the emergency department. There was no significant difference in length of hospital stay between

\[(\text{Atrovent+Plac}) \overset{V}{=} (\text{Atrovent + SABA}) \overset{V}{=} (\text{SABA alone})\]

However, combined ipratropium bromide and beta2-agonist compared to placebo showed significantly improved clinical scores at 24 hours. Well designed studies are required to clarify the role of these agents in young children with wheeze.
HOW TELEVISION BENEFITS YOUR CHILDREN

Motorola, leader in television, shows how TV can mean better behavior at home and better marks in school!

"New, sweet TV home! Peace! Quiet! No more "naughty day class..." with television being spared by out of mischief... and out of mother's sight. And that's just out of many TV listeners. Taking over television from children who 'sat up' in a punishment that really works, we're an authority on child psychology. "The very thought of missing even one program turns little faces to frowns. And, incidentally, those family programs in the late afternoon are the world's largest target for getting stubby young ones home on time."

Will television strengthen family ties? Discussions, religious and social workers, alike agree it can be one of the strongest bonds in bringing the family together. Major goal, after entertainment right in the home. Parents can select their children's "TV diet" from a wide variety of wholesome programs.

Motorola TELEVISION
ALSPAC, 26% of 6265 infants had at least 1 episode of wheeze by the age of 18 mths. (9)

Classification

• **Epidemiological:** patterns such as transient early and persistent (9,13) can be determined only retrospectively and give no guide to treatment, so are not useful for the clinician.

• **Atopic versus non-atopic:** early aeroallergen sensitisation is certainly predictive of ongoing symptoms and loss of lung function at school age, (14) but does not predict the response to treatment with inhaled corticosteroids (15).

• **Symptom pattern:** the European Respiratory Society Task Force (1)
  - **Episodic viral wheeze (EVW):** the child wheezes only with usually clinically diagnosed viral upper respiratory infections and is otherwise totally symptom free.
  - **Multiple trigger wheeze (MTW):** the child wheezes with clinically diagnosed upper respiratory infections but also with other triggers, such as exercise and smoke and allergen exposure.
Managing wheeze in preschool children

Prophylactic Continuous Inhaled Corticosteroids In Episodic Viral Wheeze?

• No evidence for regular ICS in preschool children who do not wheeze between viral colds.
• Really severe episodic wheeze with repeated admissions or prolonged disruptive symptoms managed at home, however, a trial of prophylactic inhaled corticosteroids can be given.
• Clinical trials of ICS in episodic viral wheeze done in relatively mildly affected children, so the evidence in severely affected children is less robust.
• Treatment should be reviewed and discontinued if there is no benefit;
• If the viral wheezing improves on Rx, still should still try to reduce the dose.
• Small study, even really severe episodic viral wheeze was not associated with eosinophilic airway inflammation (4)
• ICS (FP 100 μg twice a day) led to growth suppression in the PEAK trial, (21)

285 children ages 2 to 3 years RDBPC daily ICS (88ugm FP bd) v Placebo for two years. Then observed for an additional year

Inhaled corticosteroids did not alter the natural course of disease in children who began daily Rx at 2 or 3 years of age After a year without treatment - same frequency and severity of asthma-related Sx and similar levels of lung function

During the two-year treatment period, however,

Rx group - had significantly fewer and less severe asthma symptoms

• had on average 2 days of Sx per month compared to 4 days of Sx per month in the placebo group.
• lower rate of severe asthma exacerbations requiring additional treatment with oral corticosteroids and
• had less need for leukotriene receptor antagonists or additional inhaled steroid treatments.

However ICS group temporarily slow the growth of the children in the treatment group;

significant during the first year of the study, but not during the second year of treatment.

During the third-year observation period, Rx group grew more quickly

Overall, the placebo group grew an average of 1.1 cm more than the treatment group after two years,

but by the end of the three-year study, the difference in average increase in height dropped to 0.7 cm.

Guilbert et al. NEJM 2006
Montelukast And Pre-school Wheeze

The PREEMPT intermittent Montelukast v Placebo in 220 children aged 2-14. (27)

- fewer unscheduled consultations for asthma (OR 0.65, 95% CI 0.47 to 0.89)
- fewer days away from school or childcare and
- less time off work for parents (37% and 33%, respectively; P<0.001 for both).

The benefits were greater in children aged 2-5 (about 80% of the study group).

Not confirmed in 3 way comparison of intermittent montelukast, continuous montelukast, and placebo (nearly 600 children in each group). (28)

Standard treatment v intermittent montelukast v and intermittent nebulised budesonide

238 children aged 12-59 months showed minor and equivalent benefits for the two active treatments compared with standard treatment. (29)

Benefits were greater in the subgroup with a modified asthma predictive index.

Taken together, these studies suggest that a trial of montelukast in preschool children with troublesome viral induced wheeze is worth attempting.

ICS And Episodic Viral Preschool Wheeze

1. The Cochrane intermittent ICS partially effective strategy for episodic PSW. (30)

2. 129 children aged 1-6 years - pre-emptive FP 750 μg bd up to 10 days, with viral URTI (31),
   - less rescue prednisolone (8% FP group v 18% placebo; OR 0.49, 95% CI 0.30 to 0.83).
   This huge dose, however, was unsurprisingly associated with side effects and cannot be recommended.

1. Regular bd neb budesonide 0.5 mg cf intermittent neb budesonide 1 mg bd for URTI (32)
   - RDBC (nil placebo) N=278, aged 12 - 53 months, +ve mod’d asthma predictive index.
   - There was no difference in any respiratory outcome.

What this study definitely shows is that regular nebulised budesonide does not prevent viral exacerbations of wheeze.
Summary points

• Preschool wheeze should be divided into “episodic viral” and “multiple trigger” according to the history, and these categories, which can change over time, should be used to guide treatment.
• No treatment has been shown to prevent progression of preschool wheeze to school age asthma, so treatment is driven solely by current symptoms.
• In all but the most severe cases, episodic symptoms should be treated with episodic treatment.
• If trials of prophylactic treatment are contemplated, they should be discontinued at the end of a strictly defined time period because many respiratory symptoms remit spontaneously in preschool children.
• Prednisolone is not indicated in preschool children with attacks of wheeze who are well enough to remain at home or in many children who are admitted to hospital, especially those with episodic viral wheeze.
According to repeated nationwide surveys,

More Doctors Smoke CAMELS
than any other cigarette!

Doctors in every branch of medicine were asked, "What cigarette do you smoke?"
The brand named most was Camel!

You'll enjoy Camelts for the same reasons so many doctors do. Camelts have cool, smooth smoke, pack after pack, and a flavor unmatched by any other cigarette. Make this possible, too - Smoke only Camelts for 30 days and see how well Camelts please your taste. How well they suit your throat as your mouth smokes. You'll see how enjoyable a cigarette can be!

THE DOCTORS' CHOICE IS AMERICA'S CHOICE!

For 30 days, test Camelts in your "T-Zone" (T for Throat, T for Taste).
In school-age children, the ‘classical’ atopic asthma phenotype predominates. Skewing of pulmonary T cells to a Th2 phenotype, increased total and aeroallergen specific IgE, and increased airway eosinophils. (4,5)

In children aged between 1 and 5 years - frequently characterised by transient episodes of wheeze trigged by viral colds, with few or no interval symptoms (preschool viral wheeze).

Cogswell et al (10,11) babies (N = 67) at increased atopic risk - 11-years wheeze in the first 2 years of life is not a risk factor for atopic asthma in later childhood.

Martinez et al. (12) Tuscon (N= 800) children from birth - 3 wheezing pattern at 6 years of age:
(1) transient wheeze (2) late-onset wheeze (3) persistent wheeze;

Transient wheeze was not associated with any of the early markers of atopy.
Persistent wheeze had associated risk factors for classical, atopic asthma (elevated cord blood IgE and maternal history of asthma).
# Controversies in the management of preschool viral wheeze

Jayachandran R. Panickar* and Jonathan Grigg

## Table 1 Inhaled corticosteroids

<table>
<thead>
<tr>
<th>Study</th>
<th>Year and N</th>
<th>Selection criteria</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al.(^{17})</td>
<td>1995, N = 41</td>
<td>Age: 8 m to 6 years Episodic viral wheeze</td>
<td>Budesonide (400 µg/day) vs placebo for 4 months</td>
<td>Mean daily symptom score</td>
<td>No difference</td>
</tr>
<tr>
<td>RDBPC parallel group study</td>
<td></td>
<td></td>
<td></td>
<td>Mean score/episodes</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms between episode</td>
<td>No difference</td>
</tr>
<tr>
<td>Wilson et al.(^{20})</td>
<td>1990, N = 35</td>
<td>Age: 1–5 years Episodic asthma No trigger defined</td>
<td>BDP (750 µg/tds) vs placebo for 5 days</td>
<td>Symptom score</td>
<td>Significantly reduced in treatment (BDP) group</td>
</tr>
<tr>
<td>RDBPC cross-over study</td>
<td></td>
<td></td>
<td></td>
<td>Parental opinion</td>
<td>Significantly more parents felt BDP to be helpful</td>
</tr>
<tr>
<td>Connell et al.(^{18})</td>
<td>1993, N = 32</td>
<td>Age: 1–5 years Viral-induced wheeze</td>
<td>Intermittent budesonide (800 or 1600 µg/bd) vs placebo</td>
<td>Symptom score</td>
<td>Mean day- and night-time wheeze significantly lower in treatment (budesonide) group in the first week after infection</td>
</tr>
<tr>
<td>RDBPC cross-over study</td>
<td></td>
<td></td>
<td></td>
<td>Parental preference for inhaler</td>
<td>Significantly increased preference for budesonide</td>
</tr>
<tr>
<td>Svedmyr et al.(^{19})</td>
<td>1999, N = 55</td>
<td>Age: 1–3 years Asthma exacerbation No trigger defined</td>
<td>Budesonide vs placebo for 10 days</td>
<td>Symptom score</td>
<td>Significantly lower in children treated with budesonide</td>
</tr>
</tbody>
</table>

bd, twice daily; RDBPC, randomized, double-blind, placebo-controlled; tds, three times a day; µg, microgram.
Controversies in the management of preschool viral wheeze

Jayachandran R. Panickar* and Jonathan Grigg

Table 2 Oral prednisolone

<table>
<thead>
<tr>
<th>Study</th>
<th>Year and N</th>
<th>Selection criteria</th>
<th>Intervention</th>
<th>Out come measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Csonka et al.\textsuperscript{23}</td>
<td>2003, N = 230</td>
<td>Age: 6 m to 35 m</td>
<td>Oral prednisolone vs placebo for 3 days</td>
<td>Development of severe respiratory symptoms requiring additional asthma medication</td>
<td>Significantly less in prednisolone group 18% vs 37% ((P = 0.018))</td>
</tr>
<tr>
<td>RDBPC trial</td>
<td></td>
<td>Viral wheeze</td>
<td></td>
<td>Hospitalization rate from emergency department</td>
<td>No difference</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Length of hospital stay</td>
<td></td>
</tr>
<tr>
<td>Oommen et al.\textsuperscript{24}</td>
<td>2003, N = 217</td>
<td>Age: 1-5 years</td>
<td>Oral prednisolone vs placebo for 5 days</td>
<td>Symptom score</td>
<td>No difference</td>
</tr>
<tr>
<td>RDBPC trial</td>
<td></td>
<td>Viral wheeze</td>
<td></td>
<td>Mean salbutamol actuations per day</td>
<td>No difference</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Substitution of trial medication with prednisolone</td>
<td>No difference</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parental preference</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospital admission</td>
<td>More in prednisolone group</td>
</tr>
<tr>
<td>Webb et al.\textsuperscript{25}</td>
<td>1986, N = 38</td>
<td>Age: 3 m to 17 m</td>
<td>Oral prednisolone vs placebo for 5 days</td>
<td>Symptom score</td>
<td>No difference</td>
</tr>
<tr>
<td>DB partial cross-over trial</td>
<td></td>
<td>Viral wheeze</td>
<td></td>
<td>Parental preference</td>
<td>No difference</td>
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RDBPC, randomized, double-blind, placebo-controlled.
Inhaled Steroids
Taken together, these data suggest that modest improvement in symptoms might be achieved using episodic, relatively high-dose inhaled corticosteroids, but that regular inhaled steroids at normal doses, have little impact on attacks.


Oral Steroids
In summary,
There is no evidence for the routine use of intermittent oral steroids in PVW. The trial by Csonka et al. (23) shows that there may be a role for oral steroids in hospital.

For a better start in life
start COLA earlier!

How soon is too soon?

Not soon enough. Laboratory tests over the last few years have proven that babies who start drinking soda during that early formative period have a much higher chance of gaining acceptance and “fitting in” during those awkward pre-teen and teen years. So, do yourself a favor. Do your child a favor. Start them on a strict regimen of sodas and other sugary carbonated beverages right now, for a lifetime of guaranteed happiness.

The Soda Pop Board of America
1515 W. Hart Ave. - Chicago, ILL.
In the young child presenting for the first time with viral induced wheeze we have no method to distinguish between the minority with “infantile asthma” from the majority with bronchiolitis unless a bronchodilator trial is initiated.

A short course of corticosteroid may be indicated for wheeze predominant patients presenting in moderate to severe respiratory distress who demonstrate a marked improvement in wheeze following a bronchodilator trial.
“At its core EBM relies upon randomized, placebo controlled clinical trials and statistical analyses to describe differences in mean outcomes between treated and untreated groups of patients with the same disease.

The underlying hypothesis of EBM is that drug response is homogenous, i.e., that the mean response in the treatment group represents the response of any individual. By definition outliers are not reported and are ignored.

The author then goes on to discuss the importance of outliers for those who want to utilize EBM derived data to treat patients.

He argues that if outliers are very rare (< 1%) then the average response does, in fact, describe the response of individuals.

On the other hand if outliers are very common, say close to 50%, then EBM derived data would never enter into clinical practice.

However, if outliers are neither rare or common (e.g., about 10-15%) then the situation becomes very complicated and providers will need to take into account cost, drug side effects, etc. [12]”

Many school age children with known asthma began to have recurrent wheeze at a much younger age when they were in the bronchiolitis age range \(^{[14, 15]}\).

Thus while it is true that most very young infants who have had viral induced wheeze do not end up having asthma a significant clinical minority do.

In fact the percentage of such infants in the Martinez article of 1995 was 14% of all infants who had wheeze prior to 3 years of age, \(^{[14]}\).

Children with mild manifestations of bronchiolitis usually require no specific therapy.

However, wheeze predominant patients in the bronchiolitis age range presenting with moderate to severe respiratory distress should have a trial of inhaled bronchodilator with continuation for those who show significant clinical improvement.

Corticosteroid therapy should not be used except for the minority of patients presenting with respiratory distress who show a major improvement in wheeze and other signs and symptoms following a bronchodilator trial.


I'M SENDING CHESTERFIELDS to all my friends. That's the merriest Christmas any smoker can have—Chesterfield mildness plus no unpleasant after-taste

Ronald Reagan

see RONALD REAGAN
starring in "HONG KONG" a Fine-
Thomas Paramount Production
Color by Technicolor

CHESERFIELD

Buy the beautiful Christmas-card carton
Steroids not indicated in majority of Pre-school wheeze
Determining who has Episodic Viral Wheeze V Multi Trigger Wheeze is sometimes retrospective
ICS may be TRIALLED in intermittent severe EVW or very frequent presenters
Reliever Medication
• ½ days of the month / season
• ED presentations once a month
• Ward Admissions once every 3 months
• HDU / ICU admissions once a year