THE WHEEZY CHILD - WHAT IS THE EVIDENCE FOR STEROIDS?

Dr Tim McDonald

09/11/2019 National Museum of Australia

IMAGINE BETTER

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Is Orange The New Black ?

Is Orange The New Black ?

Definition Of Childhood Asthma

- "In what time does the pecularity 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 pecularity 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

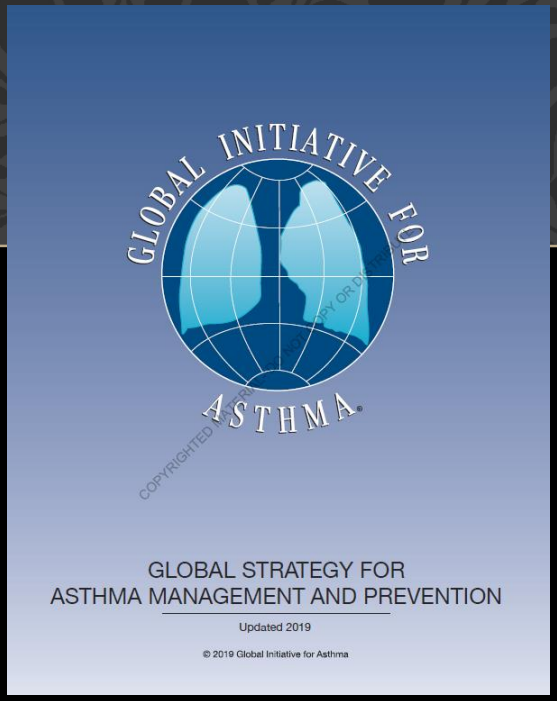
- "Recurrent, Reversible, Small airways narrowing"

McDonald 1998

ASTHMA

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)

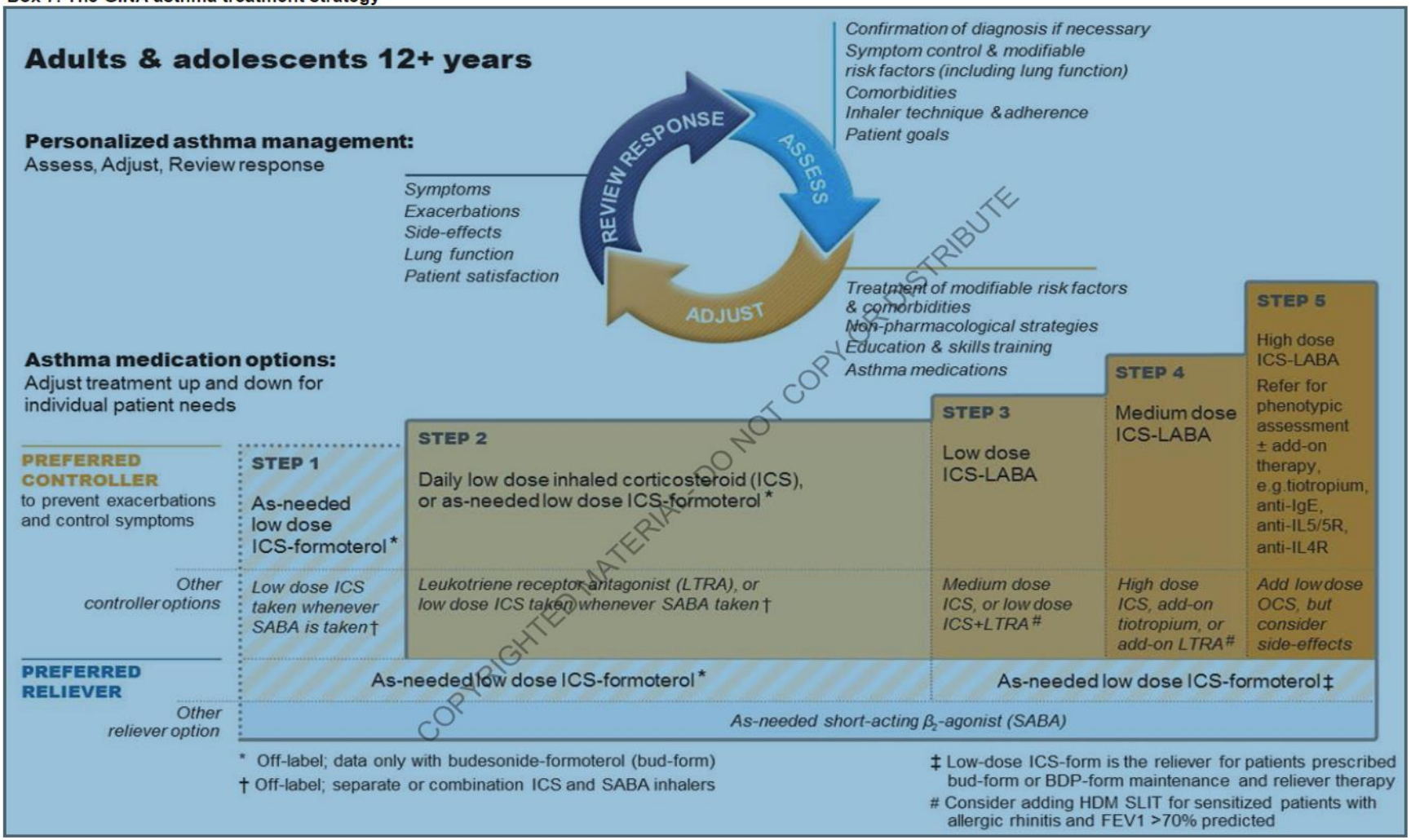
In pre-school children, recent studies suggest that clinical and/or inflammatory features may predict better short-term response to ICS, but more studies are needed (p.139). Early referral is recommended if the child fails to respond to controller treatment.

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.

ASTHMA

Box 7. The GINA asthma treatment strategy



For children 6–11 years, the preferred Step 3 treatment is low dose ICS-LABA or medium dose ICS.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Definition Of Bronchiolitis

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]

[1]. Ralston S.L.,. Pediatrics 2014; 134: pp. e1474-e1502
[2]. National Institute for Health and Care Excellence (NICE). 2015
[10]. Hancock D.G., et al: Ped Pulmonol 2017; 52: pp. 1234-1240
[11]. Meissner H.C.: Viral bronchiolitis in children. NEJM 2016; 374: pp. 62-72

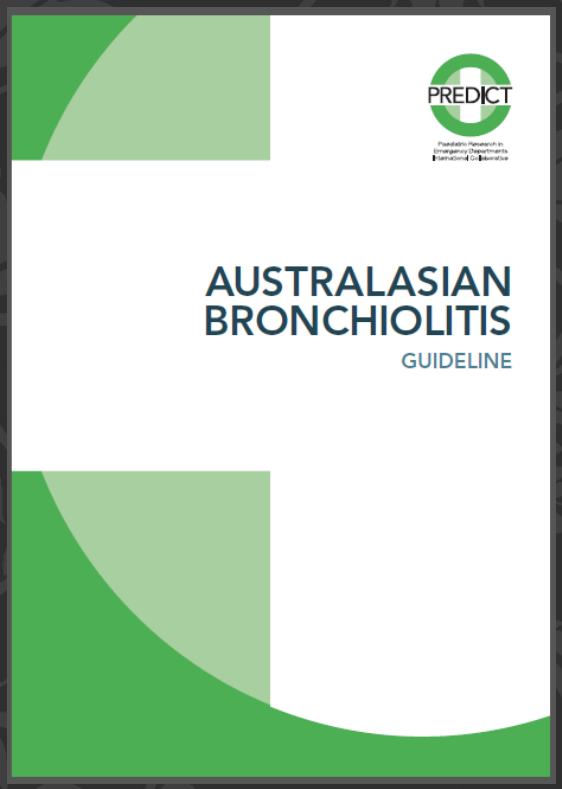
[Contemporary Reviews in Critical Care Medicine]

CHEST

CPAP and High-Flow Nasal Cannula Oxygen in Bronchiolitis

Ian P. Sinha, PhD; Antonia K. S. McBride, MBChB; Rachel Smith, MBChB; and Ricardo M. Fernandes, MD

CHEST 2015; 148 (3): 810 - 823



CrossMark

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]

Improving Evidence Based Bronchiolitis Care
Cahill And Cohen • 2018 Vol. 19, No. 1

BRONCHIOLITIS

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

PREDICT Australasian Guidelines – Nov 2016

Inhaled Steroids For Episodic Viral Wheeze Of Childhood
Cochrane Database Of Systematic Reviews; 2000

- 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.

Glucocorticoids For Acute Viral Bronchiolitis In Infants And Young Children Cochrane Database Of Systematic Reviews; 2013

- 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

Anticholinergic Drugs For Wheeze In Children Under The Age Of Two Years Cochrane Database Of Systematic Reviews: 2005

- 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

  (Atrovent+Plac) V (Atrovent + SABA) V (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.

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Managing wheeze in preschool children

Andrew Bush *professor of paediatrics and head of section (paediatrics)*[1] *professor of paediatric respirology*[2] *consultant paediatric chest physician*[3], Jonathan Grigg *professor of paediatric respiratory and environmental medicine*[4], Sejal Saglani *reader in paediatric respiratory medicine*[3 5]

[1]Imperial College, London UK; [2]National Heart and Lung Institute, Imperial College, London, UK; [3]Respiratory Paediatrics, Royal Brompton Harefield NHS Foundation Trust, London, UK; [4]Blizzard Institute, Barts and the London Hospital, London, UK; [5]Leukocyte Biology, NHLI, Imperial College London, UK

thebmj

BMJ 2014;348:g15 doi: 10.1136/bmj.g15 (Published 4 February 2014)

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

thebmj

BMJ 2014;348:g15 doi: 10.1136/bmj.g15 (Published 4 February 2014)

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]

4 Sonnappa S, Bastardo CM, Saglani S, Bush A, Aurora P. Relationship between past airway pathology and current lung function in preschool wheezers. *Eur Respir J* 2011;38:1431-6.

21 Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.

Peak Trial

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.

27 Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;175:323-9.

28 Valovirta E, Boza ML, Robertson CF, Verbruggen N, Smugar SS, Nelsen LM, et al.Intermittent or daily montelukast versus placebo for episodic asthma in children. *AnnAllergy Asthma Immunol* 2011;106:518-26.

29 Bacharier LB, Phillips BR, Zeiger RS, Szefler SJ, Martinez FD, Lemanske RF Jr; CARE Network. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-35.

Managing wheeze in preschool children

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BMJ 2014;348:g15 doi: 10.1136/bmj.g15 (Published 4 February 2014)

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.

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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,

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Controversies in the management of preschool viral wheeze

Jayachandran R. Panickar* and Jonathan Grigg

Paediatric Respiratory Reviews

PAEDIATRIC RESPIRATORY REVIEWS (2006) **7**, 293–298

- 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

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Table 1 Inhaled corticosteroids

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

bd, twice daily; RDBPC, randomized, double-blind, placebo-controlled; tds, three times a day; μg, microgram.

Controversies in the management of preschool viral wheeze

Paediatric Respiratory Reviews

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Table 2 Oral prednisolone

Study	Year and *N*	Selection criteria	Intervention	Out come measures	Results
Csonka *et al.*[23] RDBPC trial	2003, *N* = 230	Age: 6 m to 35 m Viral wheeze	Oral prednisolone vs placebo for 3 days	Development of severe respiratory symptoms requiring additional asthma medication	Significantly less in prednisolone group 18% vs 37% ($P = 0.018$)
				Hospitalization rate from emergency department	No difference
				Length of hospital stay	Shorter in prednisolone group 2 vs 3 days ($P = 0.060$)
				Duration of symptoms	Significantly less in prednisolone group
Oommen *et al.*[24] RDBPC trial	2003, *N* = 217	Age: 1–5 years Viral wheeze	Oral prednisolone vs placebo for 5 days	Symptom score	No difference
				Mean salbutamol actuations per day	No difference
				Substitution of trial medication with prednisolone	No difference
				Parental preference	No difference
				Hospital admission	More in prednisolone group
Webb *et al.*[25] DB partial cross-over trial	1986, *N* = 38	Age: 3 m to 17 m Viral wheeze	Oral prednisolone vs placebo for 5 days	Symptom score	No difference
				Parental preference	No difference (No difference for the whole group or with in subgroups 6–12 m and 12–18 m)

RDBPC, randomized, double-blind, placebo-controlled.

Controversies in the management of preschool viral wheeze

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Paediatric Respiratory Reviews

PAEDIATRIC RESPIRATORY REVIEWS (2006) **7**, 293–298

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.

17. Wilson N, et al. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. Arch Dis Child 1995; 72: 317–320.
18. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. Arch Dis Child 1993; 68: 85–87.
19. Svedmyr J, et al. Prophylactic intermittent treatment with ICS of asthma exacerbations due to airway infections in toddlers. Acta Paediatr 1999; 88: 42–47.
20. Wilson NM, et al Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Arch Dis Child 1990; 65: 407–410.

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.

23. Csonka P, et al. Oral PNL in the acute management of children age 6 to 35 months with viral LRTI induced airway disease: RBPCT. J Pediatr 2003; 143: 725–730.
24. Oommen A, Efficacy of a short course of parentinitiated oral prednisolone for viral wheeze in children aged 1–5 years: RCT. Lancet 2003; 362: 1433–1438.
25. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. Arch Dis Child 1986; 61: 15–19.


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Some Infants Who Meet The Criteria For The Diagnosis Of Bronchiolitis Should Receive A Trial Of Asthma Type Therapy

- 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.

Some Infants Who Meet The Criteria For The Diagnosis Of Bronchiolitis Should Receive A Trial Of Asthma Type Therapy

"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] "

[12]. de Leon J.: Evidence based medicine versus personalized medicine: are they enemies. J Clin Psychopharmacology 2012; 32: pp. 153-164

Some Infants Who Meet The Criteria For The Diagnosis Of Bronchiolitis Should Receive A Trial Of Asthma Type Therapy

- 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.

[14]. Martinez F.D., Al Wright, and Taussig L.M.: Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332: pp. 133-138
[15]. Garcinuno A., and Gandarillas I.: Early patterns of wheezing in asthmatic and non-asthmatic children. Eur Resp J. 2013; 42: pp. 1020-1028


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Chesterfield
CIGARETTES
CHESTERFIELD
Chesterfields for Christmas
CHESTERFIELD
CHESTERFIELD
Buy the beautiful "Christmas-card" carton

SUMMARY

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