Management of wheezy infants and preschool children

This second article in a two-part series on wheeze in children focuses on the management of the more common causes in infants (aged under 1 year) and preschool children (aged 1 to 4 years) using the best available published evidence.

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In this article, the five levels of evidence used to discuss management recommendations are based on the NHMRC's quality of evidence rating, and summarised in Table 1. Features of the common underlying causes of wheeze in infants and preschool children are noted in Table 2. The appropriate investigations for these causes were described in the first article of this series (see the June issue of *Medicine Today* 2003; 4(6): 20-27).

Management of acute viral bronchiolitis

Acute viral bronchiolitis is by far the most common cause of acute wheeze in infancy. It is usually due to respiratory syncytial virus (RSV) and is prevalent in the community each winter. Infants with acute viral bronchiolitis will have mild fever, rhinorrhoea, dry cough, plus varying degrees of wheeze and/or respiratory difficulty. It is a self-limiting illness and most infants are managed at home with no specific treatment. The usual indication for admission to hospital is the inability to maintain adequate fluid intake.

Apnoea occurs in a small percentage of children, particularly in the early stages of the illness, in preterm infants, and in very young infants. Apnoea is an absolute indication for hospital admission.

The goals of hospital in-patient management are to ensure adequate oxygenation and hydration. Supplementary oxygen (by face mask or nasal prongs) is used to relieve breathlessness and maintain oxygen saturation above 94% (on pulse oximetry). If the infant is feeding satisfactorily while receiving supplementary oxygen no further management apart from monitoring and appropriate nursing care is required. For those infants unable to feed satisfactorily despite oxygen, intravenous fluids will be required plus closer nursing observations. Fortunately, intubation

IN SUMMARY

- **Most wheezy infants have acute bronchiolitis or transient early wheezing, neither of which generally warrants any specific therapy.**
- **Age has a significant bearing on the patient's response to inhaled bronchodilators.**
- **Bronchodilators should not be used routinely for first-time wheezy infants with presumed acute viral bronchiolitis.**
- **Toddlers with wheezing associated respiratory infection (WARI) should be given a trial of inhaled bronchodilator as required.**
- **Infants and preschool children with persistent or frequently recurrent wheezing deserve a trial of long term preventive therapy with inhaled corticosteroids or a nonsteroidal preventer.**

and mechanical ventilation are rarely needed – the two major risk factors for such intervention are chronic lung disease of prematurity and very young age of the infant (under 4 to 6 weeks).

Inhaled bronchodilators

Since the small airways obstruction results from mucosal oedema and not bronchospasm, no response to bronchodilator would be expected. The role of inhaled bronchodilators (both β-agonists and anticholinergics) in infants with acute viral bronchiolitis has been the topic of a meta-analysis of randomised controlled trials (RCTs). In eight trials involving 394 children there was modest short term improvement in clinical score with bronchodilators, but no improvement in outcomes important to patients (hospitalisation rate and duration of hospitalisation).

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Unfortunately, there is potential for harm. One of the RCTs reported a substantial drop in oxygen saturation in infants given a β_2-agonist compared with placebo. Further, attaching infants to a noisy, misty nebuliser and face mask or a puffer, spacer and face mask can be distressing and worsen their respiratory difficulty. Thus, on current evidence, bronchodilators should not be used for routine management of first-time wheezy infants with presumed acute viral bronchiolitis (level 1 evidence).

However, because there is often diagnostic difficulty differentiating bronchiolitis from a first episode of asthma, a trial of bronchodilators may be considered, particularly if the breathlessness is severe. If a bronchodilator trial is given it is essential to get accurate measurements of respiratory rate, pulse rate and oxygen saturation immediately before and then five to 10 minutes after the inhalation. If there is a clear-cut improvement then it is reasonable to continue these inhalations. However, in most instances there will be no improvement, and no further bronchodilators should be given.

Systemic corticosteroids

The role of systemic corticosteroids in infants with acute viral bronchiolitis is also controversial. Data from six RCTs were included in a meta-analysis limited to infants hospitalised with bronchiolitis (total 347 subjects). Infants less than 2 months of age were generally excluded from these trials. The pooled analysis found infants receiving systemic cortico-steroids had a mean duration of hospitalisation statistically significantly shorter than those given placebo (-0.43 days; 95% confidence interval: -0.81 to -0.05 days).

While this appears to be a clinically irrelevant reduction, given the very large numbers of infants admitted to hospital each winter with bronchiolitis, at a population level this could translate to a substantial benefit to the healthcare system. An additional finding was a greater benefit in reduced length of stay in the more severe cases, especially in those admitted to the intensive care unit. The authors of this meta-analysis concluded that although further studies are clearly needed, systemic corticosteroids should be considered in the therapy of infants hospitalised with bronchiolitis, particularly those severely ill.

A recent Canadian RCT examined the efficacy of high dose oral dexamethasone in 70 infants (aged 2 months to 24 months; mean 6.5 months) with moderately severe bronchiolitis in the emergency department. This study included only infants with first-time wheeze and only those with moderate-to-severe breathlessness. Key outcome measures were the change in clinical score and differences in admission rates between the groups (four hours after receiving the dexamethasone or placebo). The corticosteroid group had a statistically significant improvement in clinical score, reflecting improvement in respiratory distress. Of greater interest was the substantially reduced rate of admission to hospital in the corticosteroid group (19% *v.* 44%). This translates to a number needed to treat of four (i.e. four infants with moderate-to-severe acute viral bronchiolitis need to be treated with corticosteroids to prevent one hospitalisation).

Follow up studies have found that at least 50% of infants with bronchiolitis severe enough to warrant hospitalisation

Table 1. Levels of evidence for recommendations*

Level 1	Systematic review or meta-analysis of all relevant randomised controlled trials (RCTs)
Level 2	Well designed RCTs
Level 3	Well designed observational studies (cohort or case–control)
Level 4	Consensus opinion

* Simplified from the NHMRC's quality of evidence rating.

will subsequently develop asthma. Thus, a substantial proportion of infants hospitalised with bronchiolitis is presumably simply having a first episode of acute asthma.

Further, we have level 1 evidence that systemic corticosteroids are highly effective in acute asthma – in terms of both reduced need for hospitalisation and reduced length of stay in hospital. Since we cannot readily distinguish these predisposed infants, the authors of this Canadian RCT argued that all infants with moderately severe bronchiolitis should be treated with systemic corticosteroids. Thus, the group with 'asthma' rather than bronchiolitis can benefit from this proven therapy.

Further high quality RCTs in other settings, including infants less than 2 months of age but excluding those over 12 months of age, are essential before any definite recommendations are possible. It is clear, however, that systemic corticosteroids are not indicated for infants with mild acute viral bronchiolitis.

Inhaled corticosteroids

There are two RCTs of inhaled corticosteroids in acute viral bronchiolitis assessing the benefit on either the acute phase of the illness or subsequent wheezing tendency. One trial found no benefit of treatment on post-bronchiolitis wheezing, whereas the other showed a reduction in subsequent wheezing, particularly in those given inhaled corticosteroids for a more prolonged period (two months). Again, it seems likely a number of infants in this study had genuine asthma and the 'bronchiolitis' was really their first episode of asthma.

Given these conflicting data, further RCTs are necessary before any firm recommendation can be made regarding the prolonged use of inhaled corticosteroids after an episode of acute viral bronchiolitis.

Persistent or recurrent wheezing syndromes

Management of transient early wheezing

Infants who fit the clinical picture of transient early wheezing (see Table 2) should not be given any form of therapy apart from parental reassurance that the wheezing is due to relatively small and/or 'floppy' airways, will subside with time and is of no medical consequence. The wheeze of transient early wheezing is not associated with any morbidity and does not warrant any intervention; it is also not easy to imagine any intervention that could help.

Management of asthma in infants and preschool children

Although genuine asthma is uncommon in the first year of life, there is no doubt that this does occur, and several RCTs evaluating various interventions have been published.

Table 2. Features of wheeze in infants and toddlers

Infant wheeze

Acute viral bronchiolitis
- Acute wheeze and breathlessness
- Viral/coryzal symptoms
- Crackles on auscultation
- Occurs in winter
- Respiratory syncytial virus in community
- No previous wheeze
- Age under 12 months
- Generally unresponsive to asthma drug therapy
- Favourable prognosis
- Only those with severe obstruction requiring hospital admission at increased risk of subsequent wheeze/asthma

Transient early wheeze
- Recurrent or persistent wheeze in infancy
- Otherwise well and thriving
- Wheeze not associated with shortness of breath, troublesome cough or need for hospitalisation
- Favourable prognosis
- Age under 12 months
- No response to any drug therapy

Infant asthma
- Recurrent wheeze with other symptoms (shortness of breath, distressing cough, may need hospitalisation)
- Wheeze on auscultation – no crackles
- Coexistent eczema and/or allergic rhinitis
- Positive family history (asthma and atopy)
- Uncommon in first year of life

Toddler/preschooler wheeze

Wheeze associated with respiratory infection (WARI)
- Wheeze only with acute viral respiratory infection
- Generally mild and infrequent

Asthma
- Recurrent wheeze
- Positive family history of atopy (first degree relatives)
- Clear cut, immediate response to inhaled bronchodilator

Foreign body inhalation
- May have history of inhalation
- Reduced breath sounds and wheeze localised to side of foreign body
- Chest x-ray may show unilateral air trapping (expiratory film)

Beta$_2$ agonists

The use of salbutamol (Ventolin, Airomir, Asmol, Epaq Inhaler) has been studied in a crossover trial of 80 infants under 1 year of age with persistent or recurrent wheeze and a personal or family history of atopy. Children were randomised to either salbutamol or placebo administered three times per day (via a puffer, spacer and mask) for two months before crossing over to the opposite therapy. This trial is a significant advance over earlier studies of wheezing infants, which were single-dose studies. In this crossover trial, there was no difference in mean daily symptom scores (cough and wheeze) between the salbutamol and placebo periods. Nor was there any difference in the number of symptom-free days. The authors of this RCT conclude that wheezy infants with an atopic background ('probable asthma') derive no benefit from two months' treatment with salbutamol. Thus, we have level 2 evidence indicating no benefit.

Ipratroprium bromide

A meta-analysis in the Cochrane database reviewed six RCTs (total 321 infants) in different settings. Infants with acute viral bronchiolitis or chronic lung disease of prematurity were excluded. The meta-analysis examined whether anticholinergic agents offer any additional benefit over inhaled β_2-agonists. In the emergency department setting, the combination of ipratropium bromide plus β_2-agonists was associated with a reduced need for additional treatments (with bronchodilators), but no difference in respiratory rate nor oxygen saturation. For those hospitalised, although there was a significantly improved clinical score at 24 hours in infants treated with the combination rather than the β_2-agonist alone, there was no significance difference in length of hospital stay.

These reviewers concluded that there is insufficient evidence to support the routine use of anticholinergic therapy for wheezing infants. The reviewers did point out, however, that parents preferred ipratropium bromide (Atrovent, Ipratrin, Apoven, Ipravent) over nebulised placebo for relief of their children's symptoms at home. In other words, parents apparently perceive some benefit of this agent, which was not detected in any of the hard outcome measures mentioned above.

Inhaled corticosteroids

Three published RCTs have examined the role of inhaled corticosteroids in infants with recurrent wheezing. All show a beneficial effect of inhaled corticosteroids, and included budesonide (nebulised) and fluticasone (via puffer and spacer). Compared with placebo, inhaled corticosteroids resulted in significant improvement in diary card symptom scores (cough, wheeze, shortness of breath, and need for rescue medications) plus a significant reduction in the number of acute exacerbations.

In summary, infants and preschool children with persistent or recurrent wheezing have a clinically relevant improvement with inhaled corticosteroids. Thus, these medications are recommended for young children with either frequently recurrent episodes of wheeze or persistent wheeze (level 2 evidence). The issue of potential harm from long term use of these agents in the very young remains uncertain. Until such evidence is available, the dose of inhaled corticosteroid should always be kept to the minimal dose that controls the infant's asthma. This is best achieved by regular review of the infant's progress and back-titrating the dose when it is clear the asthma is well controlled.

Table 3. Wheeze in infants and toddlers: general recommendations

Acute viral bronchiolitis

Mild:

- No treatment indicated
- Manage at home

Moderate or severe (most patients will require hospitalisation):

- Give oxygen and fluids as indicated
- Provide expert nursing observation and care
- Consider a trial of bronchodilators (preferably by puffer, spacer and mask) and assess response to first dose
- Consider a short course of systemic corticosteroids (particularly in severe, hospitalised infants)

Transient early wheeze

- No drug therapy indicated
- Provide parental reassurance regarding lack of airway/lung pathology and excellent prognosis

Wheeze associated with respiratory infection (WARI)

- Trial prn bronchodilator

Infrequent episodic asthma

- Trial prn bronchodilator

Frequent episodic asthma

- Trial a bronchodilator
- Trial a nonsteroidal preventer or inhaled corticosteroid (because of inefficiencies with aerosol therapy in this age group, doses should be equivalent to those used in older children)

Persistent asthma

- Trial a bronchodilator
- Trial an inhaled corticosteroid (because of inefficiencies with aerosol therapy in this age group, doses should be equivalent to those used in older children)

Foreign body inhalation

- Laryngoscopy, bronchoscopy plus oesophagoscopy under general anaesthesia (rigid endoscope) indicated

Summary

Most infants with wheeze do not have asthma. Most wheezy infants have either

Consultant's comment

Inadequate data makes evidence-based paediatrics more difficult to practise. Clinicians may agree with some, but not all of the conclusions reached by Dr Morris and Professor Mellis. I believe that it remains to be proven that any drug therapy is of benefit in bronchiolitis. In particular, I would not recommend the use of corticosteroids in 6-week-old children admitted to hospital with classic features of bronchiolitis due to RSV, and I would be much more concerned about the potential harmful effects of bronchodilators than seduced by the prospect of benefit.

Furthermore, it is important to reinforce that Dr Morris and Professor Mellis reiterate current recommendations that infants with bronchiolitis who are seen in general practice should not receive any drug therapy.

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mild acute viral bronchiolitis or transient early wheezing – neither of which generally warrants any specific therapy.

Infants with moderate or severe acute viral bronchiolitis needing hospitalisation will usually require supplementary oxygen, and some may benefit from systemic corticosteroids. When infants present with their first bout of acute wheeze the clinician cannot be certain whether they have acute viral bronchiolitis or the first episode of acute asthma (triggered by a virus). In this situation, systemic corticosteroids may be considered – especially in the hospital setting – but only if the breathlessness associated with the wheeze is severe. A trial of inhaled β_2-agonists and/or inhaled ipratroprium bromide (anticholinergic) is justifiable if the child is hospitalised and is in at least moderate respiratory difficulty. Assessment of the infant before and after the inhalation of bronchodilator is essential to determine whether there is any obvious benefit or harm. Routine use of bronchodilator inhalations is not recommended.

Infants and preschoolers with presumed asthma whose pattern of illness is consistent with either frequent episodic asthma or persistent asthma deserve a trial of long term preventive therapy. Examples of such are:

- inhaled corticosteroids – in a starting dose of 200 to 400 μg/day of beclomethasone (Becotide) or budesonide (Pulmicort), or 100 to 200 μg/day of fluticasone (Flixotide) via a puffer, small volume spacer and face mask
- a nonsteroidal preventer (e.g. sodium cromoglycate [Intal, Cromese Sterinebs]).

Toddlers who wheeze only with viral upper respiratory tract infections (wheezing associated with respiratory infection or WARI) have a pattern of illness consistent with infrequent episodic asthma and deserve a trial of bronchodilator by inhalation as required. As with long term preventive aerosols, this is best accomplished by using a metered dose inhaler and small volume spacer with face mask accompanied by clear instructions on correct technique.

Age has a significant bearing on the response to bronchodilator aerosols. In short, bronchodilators are of marginal (if any) value in young infants, but are progressively more valuable in older infants and preschoolers with acute wheeze.

We have listed in Table 3 our general management recommendation for wheeze in infants and toddlers based on the best available evidence. It is clear, however, that we need more high quality RCTs to examine the role of bronchodilators and inhaled and systemic corticosteroids in various wheezing syndromes of infants and preschoolers. Until such data are available, dogmatic recommendations regarding interventions in these wheezing syndromes are impossible. In individual patients with significant symptoms, the best policy remains a simple trial of treatment, with appropriate before and after assessment. In most cases this trial will be negative and will result in cessation of the treatment. MT

A list of further reading is available on request to the editorial office.

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Further reading

1. Kellner JD, Ohlsson A, Gadomski AM, Wang EEL. Bronchodilators (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.
2. Garrison MM, Christakis DA, Harvey E, Cummings P, Davis RL. Systemic corticosteroids in infant bronchiolitis: a meta-analysis. Pediatrics 2000; 105: E441-E446.
3. Schuh S, Coates AL, Binnie R, et al. Efficacy of oral dexamethasone in outpatients with acute bronchiolitis. J Pediatr 2002; 140: 127-132.
4. Cade A, Brownlee KG, Conway SP, et al. Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis. Arch Dis Child 2000; 82: 126-130.
5. Kajosaari M, Syvanen P, Forars M, Juntunen-Backman K. Inhaled corticosteroids during and after respiratory syncytial virus-bronchiolitis may decrease subsequent asthma. Pediatr Allergy Immunol 2000; 11: 198-202.
6. Charvasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Inhaled salbutamol for wheezy infants: a randomised controlled trial. Arch Dis Child 2000; 82: 370-375.
7. Everard ML, Bara A, Kurian M, Elliot TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years (Cochrane Review). In: The Cochrane Library, Issue 1, 2003. Oxford: Update Software.
8. Charvasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Persistent wheezing in infants with an atopic tendency responds to inhaled fluticasone. Arch Dis Child 2001; 85: 143-148.
9. Bisgaard H, Gillies J, Groenewald M, Maden C. The effect of inhaled fluticasone propionate in the treatment of young asthmatic children. Am J Respir Crit Care Med 1999; 160: 126-131.