

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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In order to give the best care to patients and families, paediatricians need to integrate the highest quality scientific evidence with clinical expertise and the opinions of the family. *Archimedes* is a bimonthly section which seeks to assist practising clinicians by providing “evidence based” answers to common questions which are not at the forefront of research but are at the core of practice. Here in *Archimedes Updates*, we revisit topics which were covered in past issues and inform you of recent advances.

The electronic edition of this journal contains extra information to each of the published *Archimedes* topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies.

Readers wishing to submit their own questions—with best evidence answers—are encouraged to review those already proposed at www.bestbets.org. If your question still has not been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com.

This month the following topic has been updated:

- Does nebulised adrenaline reduce admission rate in bronchiolitis?

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Additional information on this topic is available on the ADC website (www.archdischild.com)

Does nebulised adrenaline (epinephrine) reduce admission rate in bronchiolitis?

Report by Maud Meates, Consultant Paediatrician, North Middlesex Hospital, London, UK

A 4 month old infant attends the emergency department in the late morning with bronchiolitis. It is the first episode of wheeze. Clinically, there is moderate indrawing and recession, tachypnoea (respiratory rate = 50), reasonable air movement on auscultation, and the oxygen saturation is 94% in air. You want to admit the infant, but the mother is breast feeding and keen to get home by 3 pm, when her other children get home from school. You have heard that in North America, nebulised adrenaline has been used in some cases and admission has been avoided.

Structured clinical question

In an infant with bronchiolitis [patient] does nebulised adrenaline (compared to other treatments) [intervention] reduce the need for admission [outcome]?

Search strategy

Secondary sources

Cochrane Library (2002)—“bronchiolitis”—4 systematic reviews (3 irrelevant—anticholinergics and wheeze, ribavirin, immunoglobulin); 1 protocol.

Clinical Evidence (Issue 7)—“child health—bronchiolitis”—2 systematic reviews (1 irrelevant—adrenaline not included) and 1 protocol for SR.

DARE—“bronchiolitis”—8 systematic reviews (5 irrelevant; 2 relevant SRs were by same authors—1 referenced in Cochrane and 1 referenced in journal; 1 protocol).

PubMed clinical queries

“bronchiolitis” and “epinephrine” [therapy, sensitive]—33 references (23 irrelevant to question). Of 10 relevant, 2 not randomised controlled trials.

MedLine [1966–Dec, 2000] (Ovid)

“bronchiolitis” or “bronchitis” and [“epinephrine (exp)” or “catecholamines”]; LIMIT to “clinical trial”—23 references (14 irrelevant to question).

Nine papers addressed the question of nebulised adrenaline and bronchiolitis (two of them specifically answering the question). See table 1.

Commentary

There are only two studies (Menon *et al* and Ray and Singh) that specifically answer the question, and both of these studies show a reduction in hospital admission with adrenaline; the study groups are similar to the patient in the clinical scenario.

A systematic review that includes adrenaline as one of a number of bronchodilators fails to show significant differences in outcomes compared to placebo. However, adrenaline has an α adrenergic action that is thought to be important in bronchiolitis (as well as its β adrenergic bronchodilatation effects). The positive effect of adrenaline may therefore have been diluted in the systematic review by the inclusion of agents that have little or no effect. A systematic review on the effect of adrenaline in bronchiolitis is underway (protocol in Cochrane Library¹⁰).

The Menon and Ray studies compared adrenaline with salbutamol, which is not routinely used in the UK in this condition. For this reason, data on studies comparing adrenaline to placebo in bronchiolitis are also presented. Most studies comparing the two show a benefit of adrenaline over placebo as well as benefit over pure β adrenergic agonists. There are studies showing similar benefits with α -adrenaline as well as racemic adrenaline.

It is thought that the α adrenergic properties of adrenaline are important in bronchiolitis, as the vasoconstriction of the pulmonary vessels reduces mucosal oedema and exudate, thereby reducing airway obstruction.

Only one study (Abul-Ainine *et al*) failed to show a difference between adrenaline and placebo. Only one dose of adrenaline was used, however, which may be a reason for the lack of difference. Admission rates were not examined as all patients were admitted. This study does confirm the safety of adrenaline in this condition.

Table 1 Nebulised adrenaline in bronchiolitis

Citation	Study group	Study type (level of evidence)	Outcomes	Key results	Comments and study weaknesses
Kellner <i>et al</i> (1996)	Wheeze <24 mth. Looking at a range of bronchodilators (incl adrenaline) compared to placebo	Grade A Systematic review—most studies double blind RCTs	Clinical score Hospital admission	Slight improvement in bronchodilator group, RR=0.76 (95% CI 0.6 to 0.95) No difference, RR=0.85 (95% CI 0.47 to 1.53)	May have seen a slight improvement because of inclusion of recurrent wheezers
Menon <i>et al</i> (1995)	42 first time wheezers less than 12 months. Nebulised adrenaline (2 doses) versus nebulised salbutamol	Grade A Double blind RCT	Hospital admission Oxygen saturation	Significant difference. 33% of 81% admitted. NNT=2 (95% CI 1 to 5) Significantly higher in adrenaline group at 1 h (96% v 94%)	Small study
Reijonen <i>et al</i> (1995)	100 consecutive wheezers less than 24 months admitted. Compared adrenaline, salbutamol, and placebo (normal saline)	Grade A Double blind RCT	Mean symptom score change using the Respiratory Distress Assessment Instrument (RDAI)	Significant between adrenaline and placebo (but not significant between salbutamol and placebo)	Included some recurrent wheezers
Kristjansson <i>et al</i> (1993)	29 infants (<18 mth) with acute bronchiolitis. Adrenaline versus placebo	Grade A Double blind RCT	Symptom score Oxygen saturation	Significant improvement with adrenaline Significant improvement with adrenaline	Both groups included recurrent wheezers
Bertrand <i>et al</i> (2001)	30 infants (<12 mth) with acute bronchiolitis. Adrenaline versus salbutamol	Grade A Double blind RCT	Clinical score Length of stay	Significant improvement with adrenaline of salbutamol at day 1, although by day 4, no difference At day 4, significantly less adrenaline still admitted	
Ray and Singh (2002)	91 infants (<24 mth with 1st or 2nd episode of wheeze). \pm -adrenaline 3 doses versus salbutamol	Grade A Double blind RCT	Hospital admission Clinical score, SaO ₂ , RR	6/45 v 14/46 = ARR of 17% (0.5%, 33.7%), NNT=6 (3, 200) Significant improvement in adrenaline group cf salbutamol. SaO ₂ only showed improvement after 2nd and subsequent doses, not 1st	Some infants with 2nd episode of wheeze included. 90% subjects were less than 12 mth of age (mean age 5–6 mth)
Sanchez <i>et al</i> (1993)	24 infants <1 y, with first episode of bronchiolitis. Adrenaline versus salbutamol	Grade A Double blind RCT (crossover study)	Clinical score Pulmonary mechanics	Significant improvement with adrenaline cf salbutamol, NNT=4 (95%CI 3 to 7) Significant improvement with adrenaline cf salbutamol	Mean age 4.6 mth (\pm 0.5). Patients sedated with chloral hydrate
Abul-Ainie and Luyt (2002)	38 infants (<12 mth) with bronchiolitis. \pm -adrenaline (1 dose) versus placebo (normal saline)	Grade A Double blind RCT	Clinical score SaO ₂	No significant difference No significant difference	Only 1 dose adrenaline given. All patients admitted regardless of clinical state to assess safety. No adverse events with adrenaline
Lodrup <i>et al</i> (2000)	16 infants with acute bronchiolitis, given adrenaline. Compared with 7 healthy controls	Grade C Controlled trial	Before and after lung function	Lung function in bronchiolitis reduced and improved significantly after adrenaline. Also improved clinical score	

The regimes used were 3 ml of 1/1000 adrenaline nebulised at arrival and 30 minutes later, followed by observation for at least two hours (Menon *et al*); and 0.1 mg/kg/dose given at 20 minute intervals three times and then observation for three hours (Ray and Singh).

Currently, a multicentre trial in the UK comparing nebulised adrenaline with placebo is under discussion.

► CLINICAL BOTTOM LINE

- Nebulised adrenaline reduces hospital admission in bronchiolitis.
- Nebulised adrenaline is superior to salbutamol and placebo in relieving symptoms in bronchiolitis.
- Nebulised adrenaline is safe in bronchiolitis.

1 Kellner JD, Ohlsson A, Gadomski AM, *et al*. Efficacy of bronchodilator therapy in bronchiolitis: a meta-analysis. *Arch Pediatr Adolesc Med* 1996;**150**:1166–72.

- 2 Menon K**, Sutcliffe T, Klassen T. A randomised trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis. *J Pediatr* 1995;**126**:1004–7.
- 3 Reijonen T**, Korppi M, Pitkakangas S, *et al*. The clinical efficacy of nebulized racemic epinephrine and albuterol in acute bronchiolitis. *Arch Pediatr Adolesc Med* 1995;**149**:686–92.
- 4 Kristjansson S**, Carlsen K, Wennergren G, *et al*. Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers. *Arch Dis Child* 1993;**69**:650–4.
- 5 Bertrand P**, Aranibar H, Castro E, *et al*. Efficacy of nebulised epinephrine versus salbutamol in hospitalised infants with bronchiolitis. *Pediatr Pulmonol* 2001;**31**:284–8.
- 6 Ray MS**, Singh V. Comparison of nebulized adrenaline versus salbutamol in wheeze associated respiratory tract infections in infants. *Indian Pediatr* 2002;**39**:12–22.
- 7 Sanchez I**, De Koster J, Powell R, *et al*. Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis. *J Pediatr* 1993;**122**:145–51.
- 8 Abul-Ainine A**, Luyt D. Short term benefits of adrenaline in bronchiolitis: a randomised controlled trial. *Arch Dis Child* 2002;**86**:276–9.
- 9 Lodrup Carlsen KC**, Carlsen KH. Inhaled nebulized adrenaline improves lung function in infants with acute bronchiolitis. *Respir Med* 2000;**94**:709–14.
- 10 Hartling L**, Klassen T. Epinephrine for bronchiolitis (Protocol for a Cochrane Review). *The Cochrane Library* Issue 2, 2002.