Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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.

“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 Library™).

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 1- 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>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments and study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellner et al (1996)</td>
<td>Wheeze &lt;24 mth. Looking at a range of bronchodilators (incl adrenaline) compared to placebo</td>
<td>Grade A Systematic review—most studies double blind RCTs</td>
<td>Clinical score, Hospital admission</td>
<td>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).</td>
<td>May have seen a slight improvement because of inclusion of recurrent wheezers</td>
</tr>
<tr>
<td>Menon et al (1995)</td>
<td>42 first time wheezers less than 12 months. Nebulised adrenaline (2 doses) versus nebulised salbutamol</td>
<td>Grade A Double blind RCT</td>
<td>Hospital admission, Oxygen saturation</td>
<td>Significant difference. NNT=2 (95% CI 1 to 5). Significantly higher in adrenaline group at 1 h (96% vs 94%).</td>
<td>Small study</td>
</tr>
<tr>
<td>Reijonen et al (1995)</td>
<td>100 consecutive wheezers less than 24 months admitted. Compared adrenaline, salbutamol, and placebo (normal saline)</td>
<td>Grade A Double blind RCT</td>
<td>Mean symptom score change using the Respiratory Distress Assessment Instrument (RDAI)</td>
<td>Significant between adrenaline and placebo (but not significant between salbutamol and placebo)</td>
<td>Included some recurrent wheezers</td>
</tr>
<tr>
<td>Kristjansson et al (1993)</td>
<td>29 infants (&lt;18 mth) with acute bronchiolitis. Adrenaline versus placebo</td>
<td>Grade A Double blind RCT</td>
<td>Symptom score, Oxygen saturation</td>
<td>Significant improvement with adrenaline</td>
<td>Both groups included recurrent wheezers</td>
</tr>
<tr>
<td>Bertrand et al (2001)</td>
<td>30 infants (&lt;12 mth) with acute bronchiolitis. Adrenaline versus salbutamol</td>
<td>Grade A Double blind RCT</td>
<td>Clinical score, Length of stay</td>
<td>Significant improvement with adrenaline cf salbutamol at day 1, although by day 4, no difference. At day 4, significantly less adrenaline still admitted.</td>
<td></td>
</tr>
<tr>
<td>Ray and Singh (2002)</td>
<td>91 infants (&lt;24 mth with 1st or 2nd episode of wheeze). 3 doses adrenaline versus salbutamol</td>
<td>Grade A Double blind RCT</td>
<td>Hospital admission, Clinical score, SaO2, RR</td>
<td>6/45 x 14/46 = ARR of 17% (0.5%, 33.7%). NNT=6 (3, 200). Significant improvement in adrenaline group cf salbutamol. SaO2 only showed improvement after 2nd and subsequent doses, not 1st.</td>
<td>Some infants with 2nd episode of wheeze included. 90% subjects were less than 12 mth of age (mean age 5–6 mth)</td>
</tr>
<tr>
<td>Sanchez et al (1993)</td>
<td>24 infants &lt;1 y, with first episode of bronchiolitis. Adrenaline versus salbutamol</td>
<td>Grade A Double blind RCT (crossover study)</td>
<td>Clinical score, Pulmonary mechanics</td>
<td>Significant improvement with adrenaline cf Mean age 4.6 mth (±0.5). Patients sedated with chloral hydrate.</td>
<td>Significant improvement with adrenaline of salbutamol, NNT=4 (95%CI 3 to 7).</td>
</tr>
<tr>
<td>Abul-Ainie and Luyt (2002)</td>
<td>38 infants (&lt;12 mth) with bronchiolitis. 1 dose adrenaline versus placebo (normal saline)</td>
<td>Grade A Double blind RCT</td>
<td>Clinical score, SaO2</td>
<td>No significant difference</td>
<td>Only 1 dose adrenaline given. All patients admitted regardless of clinical state to assess safety. No adverse events with adrenaline.</td>
</tr>
<tr>
<td>Lodrup et al (2000)</td>
<td>16 infants with acute bronchiolitis, given adrenaline. Compared with 7 healthy controls</td>
<td>Grade C Controlled trial</td>
<td>Before and after lung function</td>
<td>Lung function in bronchiolitis reduced and improved significantly after adrenaline. Also improved clinical score.</td>
<td></td>
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</tbody>
</table>
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.


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Arch Dis Child 2002 87: 548
doi: 10.1136/adc.87.6.548

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