Towards evidence based medicine for paediatricians

Edited by Bob Phillips

I n 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 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. In doing this, we are adapting a format which has been successfully developed by Kevin Macaw-Jones and the group at the Emergency Medicine Journal—“BestBets”.

A word of warning. The topic summaries are not systematic reviews, through they are as exhaustive as a practising clinician can produce. They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature. What Archimedes offers are practical, best evidence based answers to practical, clinical questions.

The format of Archimedes may be familiar. A description of the clinical setting is followed by a structured clinical question. (These in aid of focusing the mind, assisting searching, and gaining answers.) A brief report of the search used follows—this has been performed in a hierarchical way, to search for the best quality evidence to answer the question. A table provides a summary of the evidence and key points of the critical appraisal. For further information on critical appraisal, and the measures of effect (such as number needed to treat, NNT) books by Sackett and Moyer may help. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

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. Updates to previously published topics will be linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- Do we need to give steroids in children with Bell’s palsy?
- Is plain radiography indicated as 1st choice imaging modality in children with non-traumatic back pain?

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 hasn’t been answered, feel free to submit your summary according to the Instructions for Authors at www.archdischild.com. Three topics are covered in this issue of the journal.

- Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?
- Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis?
- Are newer macrolides effective in eradicating carriage of pertussis?

References


Bronchiolitis: evidence based challenge

It’s the end of winter in the northern hemisphere, and paediatricians at the clinical coalface may be a little bored with the unending stream of small children sounding like old smokers. Bronchiolitis provides those who are interested in practicing evidence based medicine a great challenge: it is a common problem, desperately miserable for the children and families affected, and asks a multitude of clinical questions. How should we diagnose this condition? Should we investigate the children affected? How should we intervene to improve their lot—both generally and specifically? What is the outcome over time—and in the long term?

Archimedes has frequently taken up the challenge of offering some aspects of bronchiolitis care to a review of their evidence. We would like to take this time to point out some additional and pertinent evidence based resources. On the BestBets site you can read in more detail questions of the effectiveness of DNase, and montelukast (though we are still not aware of any research on the utility of dropping saline into a small child’s nostrils). An evidence based medicine journal contains a summary of a recent wide ranging systematic review of standard therapeutic options (bronchodilators and steroids). An original review of the usefulness of diagnostic testing is also available (though not as readable). We would also urge readers not to forget that not all “snuffle and stop breathing” episodes are bronchiolitis, and offer some alternative approaches to the treatment of pertussis.

And finally we’d like to offer a further challenge. Can we advance studies of bronchiolitis beyond enrolling only tens or hundreds of children among the thousands that pour through our fingers, and achieve such numbers in therapeutic trials that we may truly be able to distinguish which therapies (if any) are helpful?
Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?

Report by
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doi: 10.1136/adc.2004.068916

Table 1 Nasogastric versus intravenous therapy in the treatment of bronchiolitis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sammartino et al (2002)</td>
<td>73 Australian infants admitted with bronchiolitis, 55 needing fluids. 37 given fluids by NGT. 18 infants needing fluids were excluded as &lt;4 months or reduced level of consciousness or apnoea or GOR reflux needing treatment</td>
<td>Uncontrolled cohort (level 4)</td>
<td>Respiratory and heart rate, SaO2 Number going on to iv fluids 15–30% received iv fluids 1–39% received NGT fluids</td>
<td>NGT “tolerated without incident” 2/37 deteriorated as illness progressed Removal of NGT did not help</td>
<td>Uncontrolled case series Excluded children &lt;4 months</td>
</tr>
<tr>
<td>Vogel et al (2003)</td>
<td>409 infants in 5 New Zealand hospitals</td>
<td>Uncontrolled cohort (level 4)</td>
<td>Percentage receiving i.v. or NGT fluids in each hospital</td>
<td>15–30% received iv fluids 1–39% received NGT fluids</td>
<td>Uncontrolled series. No comparison of outcome of NGT vs. i.v. Large variations in practice</td>
</tr>
<tr>
<td>Stocks (1980)</td>
<td>7 preterm infants (1.6–2.2 kg) measured with and without an NGT in situ</td>
<td>Controlled physiological study (level 5)</td>
<td>Nasal resistance [Rn] (measured in 7) and total airway resistance [Raw] (measured in 4)</td>
<td>Increased Rn of 50–150% with NGT in situ 30–50% increase in Raw with NGT</td>
<td>Study only of “well” preterm infants, No comment on clinical effects. Small study. Considerable measurement difficulties</td>
</tr>
<tr>
<td>Martin et al (1988)</td>
<td>8 preterm infants (1220–1740 g)</td>
<td>Controlled physiological study (level 5)</td>
<td>Change in oral/nasal airflow (measured as % total tidal volume [TV]) with and without NGT</td>
<td>Nasal TV decreased from 54% to 39% with NGT in place Total TV remained constant despite NGT</td>
<td>Small study of “well” neonates without significant lung disease</td>
</tr>
<tr>
<td>Greenspan et al (1990)</td>
<td>14 neonates &lt;2 kg, 10 neonates &gt;2 kg with either NG or orogastric tube (OGT)</td>
<td>Controlled physiological study (level 3)</td>
<td>Minute volume, pulmonary resistance</td>
<td>Reduced minute volume, increased pulmonary resistance in &lt;2 kg group with NGT. No effect vs. OGT in babies &gt;2 kg</td>
<td>Study only of “well” neonates, up to 3 kg without lung disease</td>
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</table>

Additional information on each of the topics is available on the ADC website (www.archdischild.com/supplemental)
There is some evidence\(^1\) that a NGT increases airway resistance in small preterm neonates, but not in older heavier ones.\(^2\) Total tidal volume in well neonates is not affected by an NGT.\(^3\) However, it is difficult to extrapolate from these studies to the clinical significance of an NGT in older, larger children with bronchiolitis. Expert opinion varies. Nicolai and Pohl\(^4\) and Sporik\(^5\) argue “from first principles” that the nasogastric (NG) route be avoided because of the theoretical risk of increased airway resistance. However based on the same studies cited by Sporik, Milner came to the conclusion that the NG route is acceptable in infants over 2 kg.

The case series reported by Sammartino et al and Vogel et al show that there is widespread use of the NG route in many units.\(^6\) No conclusions can be drawn from their data regarding the safety of NG fluids versus the intravenous route.

No studies were identified assessing the likelihood of electrolyte disturbance in children with bronchiolitis given intravenous rather than nasogastric fluids.

In infants with bronchiolitis, there is no good quality evidence that rehydration by the NG route is more or less safe than via the intravenous route. A randomised controlled trial is needed.

**CLINICAL BOTTOM LINE**

- There is no good quality evidence for or against the use of nasogastric fluids in infants with bronchiolitis. (Grade D)
- Physiological studies would suggest that use of a nasogastric tube be limited to infants >2 kg. (Grade D)
- Until good quality evidence is available, local guidelines should be followed. (Grade D)

**REFERENCES**

4 Nicolai T, Pohl A. Acute viral bronchiolitis in infancy: epidemiology and management. Lung 1990;(suppl):396–405

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### Table 2 Theophylline derivatives for bronchiolitis induced apnoea

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Tobias (2000)</td>
<td>7 infants with RSV associated apnoea. Gestational age 28–32 weeks. Age at presentation 14–64 days</td>
<td>Retrospective review (level 4)</td>
<td>Prevention of mechanical ventilation</td>
<td>No infant had episodes of apnoea or bradycardia from 2 to 18 hours after the initial loading dose.</td>
<td>Initial dose of caffeine base was 10 mg/kg and if further doses are needed, given as 5 mg/kg as second dose and 2.5 mg/kg as third dose.</td>
</tr>
<tr>
<td>DeBuse and Cartwright (1979)</td>
<td>1 infant with RSV positive bronchiolitis. Gestational age 29 weeks. Post conceptional age 38 weeks.</td>
<td>Case report (level 4)</td>
<td>Prevention of mechanical ventilation</td>
<td>No apnoeic episodes occurred 9 hours after administration of theophylline.</td>
<td>Oral theophylline. Loading dose of 10 mg/kg in aliquots, then 4 mg/kg 6 hrly ×24 hours followed by 1 mg/kg.</td>
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**Are methylxanthines effective in preventing or reducing apnoeic spells in infants with bronchiolitis?**

**Report by**
P Ramesh, M Samuels, University Hospital of North Staffordshire, Stoke on Trent, UK; martin.samuels@uhns.nhs.uk
doi: 10.1136/adc.2004.068825

A 2 week old infant, born at 36 weeks gestation was admitted to the paediatric ward in November with a 24 hour history of runny nose, cough, and episodes of shallow breathing and apnoeas. This was thought to be due to bronchiolitis, and the consultant paediatrician suggested starting the baby on caffeine (theophylline derivative with less side effects). As the resident middle grade doctor, I knew that caffeine has been used widely in neonatal units for apnoea of prematurity, but I wondered if there was any evidence for its use in this clinical situation.

**Structured clinical question**

**Search strategy and outcome**

Cochrane database of systematic reviews: No directly relevant study found, but there was one systematic review on the efficacy of methylxanthines in reducing apnoea of prematurity and another systematic review on the prophylactic use of caffeine to prevent postoperative apnoea following general anaesthesia in ex-preterm infants.\(^7\)

Medline plus (no limits): Search terms: Infants and bronchiolitis/respiratory syncytial virus infections/virus/infection...
and apnoe/aapnea and caffeine/xanthine/methylxanthine/ phosphodiesterase inhibitors/theophylline

There was one retrospective review and two case reports in the form of letters to the editor directly addressing the problem (table 2). There was also one randomised controlled trial on the usefulness of aminophylline in reducing apnoeas and intubation in term infants during prostaglandin E1 infusion.

Searches were performed in August 2004.

Commentary

Recurrent apnoea is a common problem in otherwise well preterm infants. By term equivalent age, infants have usually “outgrown” their tendency to spontaneous apnoea. However, with an additional stress, such as infection (for example, bronchiolitis) or administration of drugs that depress the central nervous system (for example, general anaesthesia, prostaglandin), then apnoea and oxygen desaturations can recur.

Caffeine is recognised to reduce apnoea and the need for mechanical ventilation in preterm infants with apnoea of prematurity. In addition caffeine prevents apnoea, bradycardia, and episodes of desaturation in growing preterm infants following general anaesthesia, while aminophylline, which is another widely used theophylline derivative, was found to be effective for the prevention of apnoea and intubation during prostaglandin E1 infusion in term infants (table 3). While these data are supportive, there may be significant differences in the mechanism of apnoea in general anaesthesia and viral induced apnoea.

We could only find three reports involving a total of 10 infants, all of whom were born preterm and presented with bronchiolitis associated apnoeas approximately around term equivalent age. These reports have concluded that theophylline derivatives are effective in reducing the incidence of apnoea and avoided the need for mechanical ventilation in this clinical situation (table 1).

Caffeine has a more favourable therapeutic index than aminophylline. No major adverse effects were reported from the studies included in the systematic reviews. Litteriness, tachycardia, and raised blood glucose are the common side effects, but routine drug level monitoring is not necessary at standard dosage.

While these three reports claim that the use of caffeine helped avoid intubation in infants with viral infection induced apnoea, there are no data from randomised controlled trials confirming these benefits. As intubation for apnoea in bronchiolitis is uncommon, a large multicentre trial would be needed.

<table>
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<tr>
<th>Table 3</th>
<th>Theophylline derivatives and apnoea due to other causes</th>
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<tbody>
<tr>
<td>Citation</td>
<td>Study group</td>
</tr>
<tr>
<td>Henderson-Smart and Steer (2001)</td>
<td>192 preterm infants in 5 trials</td>
</tr>
<tr>
<td>Henderson-Smart and Steer (2001)</td>
<td>78 ex-preterm infants undergoing general anaesthesia for surgery. Gestational age 30–32 weeks. Post conceptual age 40–44 weeks</td>
</tr>
<tr>
<td>Lim et al (2003)</td>
<td>42 term infants requiring PGE1 infusion for duct dependent congenital heart disease</td>
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</table>

REFERENCES


CLINICAL BOTTOM LINE

- In addition to its proven efficacy in apnoea of prematurity, caffeine has also been shown to reduce the incidence of apnoea in ex-preterm infants following general anaesthesia and in term infants following prostaglandin infusion.
- There is only limited evidence from case reports for the use of caffeine in infants presenting with bronchiolitis associated apnoeas.

Are newer macrolides effective in eradicating carriage of pertussis?

Report by R Srinivasan, T H Yeo, Llandough Hospital, Cardiff, UK: ramsrinish@doctors.org.uk

doi: 10.1136/adc.2004.068783

You are assessing a toddler who has presented with paroxysmal cough with a whoop and post-tussive vomiting. A clinical diagnosis of “whooping cough” is made and this is duly confirmed on pernasal swab cultures that reveal the growth of Bordetella pertussis.

From history, you note that he is allergic to penicillin and has been given erythromycin for a previous episode of pertussis. However, reports of increased carriage of Bordetella pertussis have been made and this is duly confirmed on pernasal swab cultures.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Level of evidence</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Langley et al (2004)</td>
<td>477 children (6 mth–16 y) with clinical symptoms of pertussis were randomised to receive either azithromycin (10 mg/kg on day 1 followed by 5 mg/kg once a day for 4 more days) or erythromycin estolate (40 mg/kg/day in 3 divided doses for 10 days)</td>
<td>Multicentre randomised controlled trial (level 1b)</td>
<td>Bacteriologic eradication: Negative cultures at the end of treatment Relapse: Positive cultures a week after end of treatment Adverse GI events: (parent completed diary)</td>
<td>Azithromycin group: 53/53 v erythromycin group: 53/53 (eradication 100%. 95% CI 93.3 –100) Azithromycin group: 0/51 (0%); 95% CI: 0–7.0 v erythromycin group: 0/53 (0%); 95% CI: 0–6.7 Azithromycin v erythromycin groups: Overall incidence of GI side effects was 18.8% v 41.2%, NNT = 4.46 Nausea (2.9% v 8.4%; 95% CI: –8.9% to –2.0%; NNT 18.1), vomiting (5.0% v 13.0%; 95% CI: –4.9% to –1.4%; NNT = 12.5) Diarrhoea (7.1% v 11.8%; 95% CI: –9.0% to –0.3%; NNT = 21.2) No serious adverse events were recorded in either group 90% in the azithromycin group v 55% in the erythromycin group</td>
<td>Group assignment not blinded after randomisation Positive Nasopharyngeal (NP) cultures for pertussis were found in 58/239 (azithromycin group) and in 56/238 (erythromycin group) Post treatment cultures not available on all subjects</td>
</tr>
<tr>
<td>Lebel and Mehra (2001)</td>
<td>153 children (&lt;16 y) with clinical symptoms of pertussis received either clarithromycin 7.5 mg/kg/dose twice a day for 7 days (n = 76) or erythromycin (13.3 mg/kg/dose three times a day for 14 days (n = 77)</td>
<td>Prospective randomised single blind trial (level 1b)</td>
<td>Bacteriologic eradication: Negative post treatment cultures</td>
<td>Negative post treatment cultures recorded in 31/31 on clarithromycin (100%; 95% CI: 88.8–100%) v 22/23 with erythromycin (96%; 95% CI: 78.1–99.9%)</td>
<td>35/76 in the clarithromycin group and 27/77 in the erythromycin group had positive cultures of B pertussis 90% of subjects were appropriately immunised against pertussis</td>
</tr>
<tr>
<td>Pichichero et al (2003)</td>
<td>34 subjects (29 culture positive and 5 per positive) were all given azithromycin (10 mg/kg on day 1 followed by 5 mg/kg once a day for 4 more days)</td>
<td>Prospective, open labelled, non-comparative trial (level 2b)</td>
<td>Bacteriologic eradication: Negative cultures/PCR at days 2–3 of treatment and days 14–21 post treatment</td>
<td>1/34 (3%) had positive cultures at 2–3 days on treatment Bacteriologic eradication 97% at 2–3 days and 100% by 14–21 days after starting treatment</td>
<td>Study group heterogeneous. No subset analysis available 5 of the 34 subjects were adults (parents of children), 12 were between 10–20 y of age and 17 were from the age of 6 mth to 10 y</td>
</tr>
<tr>
<td>Bace et al (1999)</td>
<td>37 subjects with culture proven pertussis. Mean age of patients 7.5 mth (range 2–18 mth). 60% of them were not immunised against pertussis. All received azithromycin. Dose: 10 mg/kg on day 1 followed by 5 mg/kg once a day for a day 4 more days (n = 17) v 10 mg/kg once daily for 3 days only (n = 20)</td>
<td>Prospective, open labelled, non-comparative trial (level 2b)</td>
<td>Bacteriologic eradication: Negative cultures on day 7, 14 after commencement of treatment. Relapse: Positive cultures on day 21 after start of treatment</td>
<td>Positive cultures on day 7: 2/19 in the 3 day group (10.5%) v 0/16 in the 5 day group. 100% bacterial eradication was seen on day 4/0/16 v 0/16 in both groups</td>
<td>Allocation criteria to either regime unclear Relationship of transaminits to dose used unclear</td>
</tr>
<tr>
<td>Aoyama et al (1996)</td>
<td>17 patients (0–13 y) with culture proven pertussis 8/17 received azithromycin (10 mg/kg once a day for 5 weeks) while 9/17 received clarithromycin (10 mg/kg/day in two divided doses for 7 days). Each study subject was matched with two historical controls treated with erythromycin (40–50 mg/kg/day in three divided doses for 14 days) 58.8% of subjects were not immunised against pertussis</td>
<td>Two separate open labelled trials using historical controls (level 4)</td>
<td>Bacteriologic eradication: negative culture on 1 week after treatment</td>
<td>8/8 with azithromycin (100%, 95% CI: 68.8–100%) v 13/16 (81%, 95% CI: 54.4–96%) among controls given erythromycin 9/9 with clarithromycin (100%, 95% CI: 71.1–100%) v 16/18 (88.8%, 95% CI: 65.3–98.6%) among controls given erythromycin None in either study or control groups</td>
<td>Historical controls Allocation criteria to medications unclear Small study group</td>
</tr>
</tbody>
</table>
tonsillo-pharyngitis. His mother recalls that he suffered severe abdominal pain when taking it and did not complete the course. You wonder whether newer macrolides such as azithromycin or clarithromycin could be effective alternatives to erythromycin for the treatment of pertussis.

**Structured clinical question**

In a child diagnosed with whooping cough [patient] are azithromycin or clarithromycin [intervention] compared with erythromycin [comparison] as effective in eradicating infection with fewer side effects [outcome]?

**Search strategy**

Primary source: Medline via Pubmed using keywords Pertussis OR Whooping Cough and combining the search with Azithromycin, Clarithromycin separately. This was verified by an alternative search method using MeSH heading “Whooping Cough” and subheading “drug therapy” [MeSH]. Five relevant articles were found.

Secondary sources: Cochrane database and Best Bets. No further papers were identified.

See table 4.

**Commentary**

Antimicrobials are usually administered when pertussis is suspected or confirmed. If the disease is already established (paroxysmal phase), antibiotics have little or no effect on the clinical course of the illness except to render the patient non-infectious to others. This is important, so as to limit the spread of infection especially to the unimmunised and young infants. A 10–14 day course of erythromycin is the long established treatment for whooping cough. It is known to reduce transmission and hasten clearance of B pertussis. However, gastrointestinal side effects seem quite limiting in a large proportion of patients treated with it. This may have a bearing in ensuring compliance. Newer macrolides—clarithromycin and azithromycin—are superior to erythromycin in terms of absorption, acid stability, and tissue penetration. They have longer half-lives, enabling less frequent dosing and shorter treatment courses. They are also known to have fewer side effects.

From the available evidence it can be seen that the newer macrolides are at least as effective as erythromycin in eradicating B pertussis infection. A significant reduction in adverse gastrointestinal side effects and a better compliance have been shown. No serious side effects have been observed with these agents so far. Transient elevation in alanine aminotransferease (ALT) has been shown in one study.

Regarding prophylaxis, the current UK guideline is to administer a seven day course of erythromycin, if a clinically suspected or confirmed case of pertussis is identified. The aim is to protect those at risk from pertussis: infants, especially neonates; all household contacts who are unimmunised; and contacts who are 5 years or older if they did not receive a pre-school pertussis booster. There is no evidence of any benefit from chemoprophylaxis given more than 21 days from the date of onset of the primary case. Unimmunised or partially immunised cases and contacts should complete their course of vaccine. Clarithromycin and azithromycin are potential, but not proven alternatives to erythromycin for prophylaxis at present.

**CLINICAL BOTTOM LINE**

- A five day course of azithromycin or a seven day course of clarithromycin is as effective as a 10–14 day course of erythromycin to eradicate B pertussis infection. (Grade A)
- Azithromycin and clarithromycin have fewer gastrointestinal side effects than erythromycin. (Grade A)
- Patient compliance is better on the newer macrolides compared to erythromycin. (Grade A)

**REFERENCES**