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 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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 focusing the mind, assisting search—2 and gaining answers.3) 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.4 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 Sackett5 and Moyer6 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
Is nasogastric fluid therapy a safe alternative to the intravenous route in infants with bronchiolitis?

Report by
N Kennedy, N Flanagan, Royal Belfast Hospital for Sick Children, Falls Road, Belfast BT12 6BE, UK; neilsaraben@aol.com
doi: 10.1136/adc.2004.068916

It is mid-December. As a paediatric SHO working a busy evening shift in a district general hospital, you are called to re-site the intravenous cannula of an infant with bronchiolitis. This is the fifth time that day you have been asked to perform such a task, and you approach the distressed, chubby infant with a sense of dread. Of the 20 children on the ward, 15 have bronchiolitis and 10 are on intravenous fluids. You consider how much distress placement and regular replacement of the cannulae causes these infants, and wonder if fluids could be given safely by another route. Would rehydration using a nasogastric tube (NGT) be appropriate?

Structured clinical question
In infants with bronchiolitis who need maintenance or replacement fluid therapy [subject], does administration by the nasogastric route [intervention] cause more respiratory difficulty or electrolyte disturbance [outcome] than intravenous infusion [comparison]?

Search strategy and outcome
Cochrane Library: Nil relevant
PubMed: three searches:
- “bronchiolitis” AND “nasogastric”
- “nasogastric” AND “airway” OR “airway obstruction”
- “bronchiolitis” AND “fluid” OR “rehydration” Limits: birth–18 years, human.

Search outcome: 72 papers, of which seven were relevant (see table 1). (Editorial comment by Nicolai and Politi5 and commentary of Milner5 not included in table.) Search date: March 2004.

Commentary
Maintaining optimal hydration is an important component in the management of bronchiolitis. Practice varies between units as to the route of administration.

Table 1

<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 GO reflux needing treatment</td>
<td>Uncontrolled cohort (level 4)</td>
<td>Respiratory and heart rate, SpO2 Number going on to iv 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) measured with and without an NGT</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>
</tr>
</tbody>
</table>
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.\(^6\) However, 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)

**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\(^7\) and another systematic review on the prophylactic use of caffeine to prevent postoperative apnoea following general anaesthesia in ex-preterm infants.\(^8\)

Medline plus (no limits): Search terms: Infants and bronchiolitis/respiratory syncytial virus infections/virus/infection

**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>
<th>Key results</th>
<th>Comments</th>
</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>Johnston and Kuzemko (1992)</td>
<td>2 infants 1. RSV positive Gestational age 33 weeks Post conceptional age 40 weeks 2. Echo virus type 2 Gestational age 36 weeks Post conceptional age 37 weeks</td>
<td>Case report (level 4)</td>
<td>Prevention of mechanical ventilation</td>
<td>Respiration became regular with disappearance of apnoea immediately after administration of aminophylline</td>
<td>5 mg/kg of iv aminophylline followed by 5–7 days of oral theophylline</td>
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<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 for 24 hours followed by 1 mg/kg</td>
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</tbody>
</table>

**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**

In infants with bronchiolitis [patient] does caffeine [intervention] reduce or prevent apnoeas [outcome]?
and apnoea/apnea 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. 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 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.

**REFERENCES**


Are newer macrolides effective in eradicating carriage of pertussis?

**Report by**

R Srinivasan, T H Yeo, Llandough Hospital, Cardiff, UK; ramsriniv@doctors.org.uk
doi: 10.1136/adc.2004.068783

**Y**ou 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
Table 4  Use of newer macrolides in pertussis

<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</td>
<td>Azithromycin group: 53/53 v erythromycin group: 53/53 (eradication 100%; 95% CI 93.3–100)</td>
<td>Group assignment not blinded after randomisation</td>
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<td>Relapse: Positive cultures a week after end of treatment</td>
<td>Azithromycin group: 0/51 (0%; 95% CI: 0–7.0) v erythromycin group: 0/53 (0%; 95% CI: 0–6.7)</td>
<td>Positive Nasopharyngeal (NP) cultures for pertussis were found in 58/239 (azithromycin group) and in 56/238 (erythromycin group)</td>
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<td></td>
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<td></td>
<td>Adverse GI events (parent completed diary)</td>
<td>Azithromycin group v erythromycin groups: Overall incidence of GI side effects was 18.8% v 41.2%, NNT = 4.46</td>
<td>Post treatment cultures not available on all subjects</td>
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<td></td>
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<td>Compliance: (inspection of medication containers)</td>
<td>Nausea (2.9% v 8.6%; 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)</td>
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<td>Diarrhoea (7.1% v 11.8%; 95% CI: –9.0% to –0.3%; NNT = 21.2)</td>
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<td>No serious adverse events were recorded in either group</td>
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<td>90% in the azithromycin group v 55% in the erythromycin group</td>
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<td>Label 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>
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<td>Adverse GI events</td>
<td>Seen in 45% of those on Clarithromycin. Vs 62% of those on Erythromycin. (p = 0.035; NNT = 5.8)</td>
<td>Post treatment cultures not available on all subjects</td>
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<td>Compliance: (inspection of medication containers)</td>
<td>Mean percent of drug taken by the Clarithromycin group was 98.5% Vs 88.8% by the Erythromycin group</td>
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<td>(p = 0.001)</td>
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<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</td>
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<td></td>
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<td>Adverse events</td>
<td>No serious adverse events recorded 10%: patients had GI side effects (nausea, loose stools, and abdominal discomfort)</td>
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<td>Compliance</td>
<td>Reported 100%</td>
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<td>Bace et al (1999)</td>
<td>37 subjects with culture proven pertussin. 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 or more 4 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</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 14 (0/16 v 0/16) in both groups</td>
<td>Allocation criteria to either regime unclear</td>
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<td></td>
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<td>Relapse: Positive cultures on day 21 after start of treatment</td>
<td>1/14 patients on the 3 day course (7.1%). None on the 5 day course</td>
<td>Relationship of transaminits to dose used unclear</td>
</tr>
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<td></td>
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<td></td>
<td>Adverse events</td>
<td>Transient increase in liver enzyme ALT noted in up to 20.6% of all subjects</td>
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<td>Compliance</td>
<td>Reported</td>
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<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>Bacterial 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</td>
<td>Historical controls Allocation criteria to medications unclear Small study group</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Relapse: positive culture at 2 weeks after treatment</td>
<td>None in either study or control groups</td>
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</tbody>
</table>
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


