Edited by Bob Phillips
Towards evidence based medicine for paediatricians

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.1 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. They are based on an original format from the Journal of Accident and Emergency Medicine.2

A word of warning. These best evidence topic summaries (BETs) are not systematic reviews, though 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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.

Each topic follows the same format. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,3 and gaining answers.4) 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.5 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 Sackett6 and Moyer7 may help. A commentary is provided to pull the information together, and for accessibility, a box provides the clinical bottom lines.

Readers wishing to submit their own questions—with best evidence answers—are encouraged to read the Instructions for Authors at http://www.archdischild.com. Three topics are covered in this issue of the journal.

- Does iron have a place in the management of breath holding spells?
- Is omeprazole helpful in the management of children with reflux oesophagitis?
- Does oral sucrose reduce the pain of neonatal procedures?

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REFERENCES
5 http://cebm.jr2.ox.ac.uk/docs/levels.htm 6

Economic analyses
For the uninitiated, the realm of economic analysis appears a fiery pit of sulphur, brimstone, and fiends. I am assured it doesn’t get much better after initiation. A short guide to the types of analysis follows:

- **Cost minimisation:** Reports only costs—should be used when good data support the equivalence of the options presented.
- **Cost effectiveness:** Reports the costs and clinical effectiveness of various options, using “natural units” (e.g. years of life, symptoms scores, etc). Does not include utility adjusted reports (see next).
- **Cost utility:** Reports the costs and utilities of option. Utilities are an assessment of quality of life, generally scored from 0 (worst) to 1 (best), and summarised as the equivalent number of years at utility = 1; the quality adjusted life year or QALY. Utilities are measured in various ways, for example: rating scales (“How’s life with asthma—from 0 to 10?”); time trade off (“If I could cure you of your diabetes, but you died in five years, would it be worth it? How about 10 years? 15?”); or standard gamble (“If I had a treatment for your cerebral palsy, worked perfectly in 9/10 cases but killed in 1/10, would you take it? How about if it killed in 1/100?”).
- **Cost benefit:** Report where the utilities have been given monetary values and an overview is given.

Does iron have a place in the management of breath holding spells?

Report by Robert Boon, Specialist Registrar Paediatrics, Gosford Hospital, New South Wales, Australia

A 2 year old child is seen in the outpatients department with a history of breath holding spells for the past three months, occurring about 3–4 times per week. These are causing her mother a great deal of concern. You consider whether or not a course of iron would reduce the frequency of these attacks.

Structured clinical question
In a 2 year old child with breath holding spells [patient], will a treatment with iron [intervention] reduce the frequency of episodes [outcome]?  

Search strategy and outcome
Breath holding spells AND iron therapy, limited to (English & Child)—six hits: two letters, an editorial and three papers as discussed below. See table 1.

Commentary
The literature reviewed suggests that a trial of iron therapy will reduce the frequency of breath holding spells.

All these papers showed a high incidence of iron deficiency anaemia associated with breath holding spells. A full blood count would therefore be warranted in the work up of these children. Treatment is more likely to be successful when there is concomitant iron deficiency anaemia.

Length of treatment varied between 3 and 16 weeks with ferrous sulphate (5–6 mg/kg/day). A course of 8 weeks would seem reasonable—long enough to improve any anaemia.

There was no mention of side effects with ferrous sulphate treatment in any of these papers. Typically these would include nausea, vomiting, diarrhoea, and change in stool colour; the latter presumably making it difficult to complete a double blind study of iron therapy.

There is also the risk of accidental overdose by the patient or siblings to be considered. However, the risk of overdose with adult preparations.

The decision to treat also needs to be balanced against the response to treatment with iron.

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<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td><strong>Citation</strong></td>
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<tr>
<td>Daoud et al (1997) 67 children with BHS were randomised to either ferrous sulphate or placebo</td>
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<tr>
<td>Mocan et al (1999) 91 children with breath holding spells. 63 with concomitant IDA</td>
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<td>Bhatia et al (1990) 50 children with BHS</td>
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**Is omeprazole helpful in the management of children with reflux oesophagitis?**

Report by Lizy A Varughese, Lynnette J Mazur, University of Texas Houston Medical School, Houston, TX, USA

An 18 month old boy with cerebral palsy is brought to your office because of “spitting up” after feeds. It has been a problem for the past several months, but is progressively worsening and now occurs after every meal and even at night. He was breast fed for 12 months and has slight developmental delay. Height and head circumference are between 25–50th centile, but weight is below 5th centile for age. A barium swallow reveals significant gastro-oesophageal reflux to the pharynx. A gastroscopic examination with biopsy reveals moderate oesophagitis without eosinophilia. You wonder if a proton pump inhibitor will be an effective treatment.

Structured clinical question
In children with gastro-oesophageal reflux [patients] does treatment with a proton pump inhibitor [intervention] decrease symptoms, increase gastric pH, and improve endoscopic findings [outcome]?

Search strategy and outcome

Commentary
There is adequate and consistent evidence that the proton pump inhibitor omeprazole is effective in the treatment of gastroesophageal reflux in children. In the five studies that addressed clinical outcomes, all patients had improvement in their symptoms. All of the studies addressed endoscopic outcomes and all patients had improvement in their findings after

**CLINICAL BOTTOM LINE**
- Iron therapy is of benefit in children with breath holding spells (NNT=2).
- Improvement is more likely in those with concomitant iron deficiency anaemia (NNT=1).


<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cucchiara et al [1993]</td>
<td>RCT</td>
<td>Clinical</td>
<td>Both regimens effective</td>
<td>Decreased clinical score (p&lt;0.01)</td>
<td>Double blind RCT, 7 (22%) drop out; 6 month follow up. High relapse rate after treatment; 5/15 (33%) ranitidine and 7/12 (58%) omeprazole patients were still symptomatic, 2 required antireflux surgery</td>
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<td></td>
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<td>Oesophageal pH monitoring [OpHM]</td>
<td>Decreased OpHM reflux time</td>
<td>Omeprazole: 129 (64–217) to 44.6 (0.1–128) Ran: 207 (66–306) to 58.4 (32–128)</td>
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<td>Gastroscopy (histology)</td>
<td>Decreased histologic score</td>
<td>(p&lt;0.01) Omeprazole: 8 (6–10) to 2 (0–6) Ranit: 8 (8–10) to 2 (2–6)</td>
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<td>Kato et al [1996]</td>
<td>Case-control</td>
<td>Gastroscopy</td>
<td>Benefit in biopsy (healing rate): 2 weeks 46%; 4 weeks 85%; 6 weeks 92%; 8 weeks 92%</td>
<td>Criteria for healing not clear (biopsy results not reported); No controls; No pretreatment pH studies; No treatment for patients with H pylori; 7/12 (58%) relapsed</td>
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<td>Gastric-pHM</td>
<td>Mean gastric pH Controls: 2.1 (1.8–2.5) Omepr: 5.2 (3.0–6.6) (p&lt;0.005) Cim/Fam: 3.1 (1.9–3.8) (p=0.05)</td>
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<td>Gunasekaran et al [1993]</td>
<td>Case series</td>
<td>Clinical</td>
<td>Follow up: 3 months: decreased symptoms 75%</td>
<td>No controls; 8 neurologically impaired children and 1 with CF. Gastroscopy at 6 months only done on patients with endoscopic evidence of oesophagitis at first follow up</td>
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<td></td>
<td></td>
<td>Gastroscopy</td>
<td>6 months: decreased symptoms all</td>
<td>No difference in histologic scores Decreased GOR [%; no, no &gt;5 min., and longest GOR]</td>
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<td>Omeprazole</td>
<td>9/15 had gastroscopy and all 9 improved</td>
<td>No controls; One year follow up 83% asymptomatic</td>
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<td>OpHM</td>
<td>Before treatment pH&lt;4 for 11–88% of time</td>
<td>Decreased clinical score (p&lt;0.05); Decreased score all</td>
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<td>De Giacomo et al [1997]</td>
<td>Case series</td>
<td>Clinical</td>
<td>Decreased symptoms all (p&lt;0.05) Decreased score all</td>
<td>No controls; 4 (40%) with significant comorbidities; 6 (60%) relapse after therapy; 3 required antireflux surgery</td>
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<td>Gastroscopy Histology OpHM</td>
<td>No difference in histologic scores Decreased GOR [%; no, no &gt;5 min., and longest GOR]</td>
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<tr>
<td>Alliet et al [1998]</td>
<td>Case series</td>
<td>Clinical</td>
<td>Decreased symptoms 10/12 (83%)</td>
<td>No controls; One year follow up 83% asymptomatic</td>
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<td>Gastroscopy Biopsy</td>
<td>9 (75%) had completely normal mucosa; 3 (25%) improved 8 (67%) completely healed; 4 (33%) improved</td>
<td>No controls; One year follow up 83% asymptomatic</td>
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<td>Hassall et al [2000]</td>
<td>Case series</td>
<td>Clinical</td>
<td>Decreased symptoms: 53 (93%)</td>
<td>21 (37%) neurologically impaired; 7 (12%) repaired oesophageal atresia. No treatment for patients with H pylori. No long term follow up</td>
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<td>Gastroscopy</td>
<td>Healed: 54 (98%), Median healing time 102 days</td>
<td>Decreased intragastric acidity (no p values)</td>
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<tr>
<td>Karjoo et al [1995]</td>
<td>Case series</td>
<td>Gastroscopy</td>
<td>91/129 (70%) responded to ranitidine; 38/129 (30%) non-responsive to ranitidine; 33/38 (87%) responded to omeprazole (p&lt;0.05); 5 (4%) failed both treatments (3 had Nissen fundaplications)</td>
<td>Degree of oesophagitis on gastroscopy predictive of response to ranitidine (90% of patients with grade 1 responded). No long term follow up</td>
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fact that there were more patients with comorbid conditions which looked at oesophageal pH showed an increase with treatment, which is indicative of decreased acid production. In the three studies that included children with significant comorbidities such as oesophageal atresia, neurological impairment, and cystic fibrosis, omeprazole was effective. In the four studies that had long term follow up, the relapse rates ranged from 17% to 60%. The higher relapse rates in the studies by Kato et al and De Giacomo et al could be attributed to the fact that there were more patients with comorbid conditions and untreated H. pylori infections, respectively. Based on these results, clinicians may want to consider Hassall et al’s advice that “the high degree of efficacy and safety of omeprazole defines a new standard for ‘optimised medical management’ in children. It is our opinion that in most circumstances, a trial of the new optimised medical therapy should be considered before antireflux surgery”.

▲ CLINICAL BOTTOM LINE

- When children with gastro-oesophageal reflux fail first line therapy, omeprazole is an effective second line choice. It may also be effective treatment in children with comorbid conditions such as cystic fibrosis, repaired oesophageal atresia, and neurological impairment.


Does oral sucrose reduce the pain of neonatal procedures?

Report by Nicole Horwitz, Specialist Registrar, Lister Hospital, UK

You are a junior doctor working in a neonatal intensive care unit. You are about to take blood from a baby born at 34 weeks gestation who is now 24 hours old and not being ventilated. The neonatal sister suggests you give the baby some oral sucrose before the procedure as analgesia. You have never used sucrose before and are uncertain whether there is any real evidence behind its efficacy.

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<th>Table 3</th>
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<td><strong>Citation</strong></td>
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<tr>
<td>Stevens et al (2001)</td>
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<td>Abad et al (2001)</td>
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<tr>
<td>Blass et al (1991)</td>
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<td>Blass et al (1997)</td>
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www.archdischild.com
Structured clinical question
In non-ventilated neonates [patient], does oral sucrose [intervention] reduce the pain of neonatal procedures [outcome]? 

Search strategy and outcome
Cochrane Database and Medline using PubMed interface. 
Search outcome: three systematic reviews, one relevant; 23 papers, of which 17 were relevant. Of these, 14 were included in the systematic review. See table 3.

Commentary
All 14 studies included in the Cochrane Review and the three additional studies quoted above show a significant reduction in indicators of pain when sucrose is used for analgesia in pre-term and term neonates undergoing blood sampling. The most consistent effect is the reduction in crying time. 

Few papers considered adverse effects; those that did suggested that these were minimal, including transient desaturation and choking following sucrose administration. Further work is required to elucidate the safety of oral sucrose, particularly in very low birth weight babies and others at risk of developing necrotising enterocolitis. Questions have also been raised about early conditioning to sweeteners. No such conditioning has been shown convincingly but there is concern that parents, impressed by the calming effect of sucrose, will continue to use it at home.

There is no clear consensus on adequate dose of sucrose. Doses between 0.012 g and 1 g were shown to be effective in the above studies. In all but three of the studies, sucrose was given two minutes prior to the procedure. Sucrose appears to work in a dose dependent fashion: the higher the dose the greater the reduction in pain.1 2 There were several other findings in the aforementioned studies. Many studies found that sucrose combined with the use of a pacifier has a synergistic effect on pain reduction. One study found that use of a pacifier alone was significantly more analgesic than sucrose used alone. Investigators studying whether sucrose exerts its analgesic effects through a pre- or post-absorptive mechanism found that it is ineffective when administered intragastrically and only reduced pain when given orally. Another trial found that sucrose is more effective than milk and its components in reducing pain. Finally, there is a significant synergistic effect when sucrose is combined with holding the baby throughout the procedure, suggesting that a “caregiving” context is beneficial to pain reduction in neonates.3

> CLINICAL BOTTOM LINE
• Sucrose is effective at reducing pain in neonatal procedures and should be used for venepuncture and heelstick sampling.
• 2 ml of 12–50% sucrose should be given 2 minutes before procedure.

Stevens B, Yamada J, Ohlsson A. Sucrose analgesia in newborn infants undergoing painful procedures. Cochrane Library 2001;3