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

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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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, 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. 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.

1. Does iron have a place in the management of breath holding spells?
2. Is omeprazole helpful in the management of children with reflux oesophagitis?
3. 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 your 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 etc?”).
- Cost benefit: Reports 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 paediatric preparations of iron is minimal compared with adult preparations.

The decision to treat also needs to be balanced against the natural course of breath holding spells which are invariably benign and self limiting—both in the short and long term.

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).


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

A 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 gastrooesophageal 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

Table 1

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Daoud et al [1997]</td>
<td>67 children with BHS were randomised to either ferrous sulphate or placebo</td>
<td>RCT (level 1b)</td>
<td>Frequency of BHS per month after 16 weeks</td>
<td>Complete response in 51.5% treated v 0% in non-treatment group. Partial response in 36.4% treated group v 5.9% in non-treatment group. NNT for any response = 2 (95% CI 2 to 3)</td>
<td>The baseline mean Hb in children who showed a response was 86 g/l compared to 106 g/l in those that responded poorly (p=0.004)</td>
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<td>Mocan et al [1999]</td>
<td>91 children with breath holding spells. 63 with concomitant IDA</td>
<td>Case control (level 4)</td>
<td>Frequency of BHS over the 3 months study period</td>
<td>Complete response in 32% treated group and 21% more had partial response. NNT (for either a partial or complete response) = 2 (95% CI 2 to 3)</td>
<td>Only those children with BHS and IDA were treated with iron. The placebo group were those with BHS but normal Hb</td>
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<tr>
<td>Bhatia et al [1990]</td>
<td>50 children with BHS</td>
<td>Case series (level 4)</td>
<td>A reduction in frequency and severity of BHS following a course of iron which was continued until Hb &gt;11 g/dl</td>
<td>96% of the study group had IDA [mean Hb = 8.12 g/dl]. 82% showed a response within 2 weeks. After three weeks 100% of cases had shown an improvement</td>
<td>Failed to define improvement</td>
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<tr>
<td>Cucchiara et al (1993)</td>
<td>32 children (6 months to 13 years) with severe reflux oesophagitis and failed ranitidine and cисapride. Patients randomised to high dose ranitidine (20 mg/kg/day) or omeprazole (40 mg/day/1.73m²) for 8 weeks</td>
<td>RCT</td>
<td>Clinical</td>
<td>Both regimens effective. Decreased clinical score (p&lt;0.01) Omepr: 24 (15–33) to 9 (0–18) Ran: 19.5 (12–33) to 9 (6–12) Decreased OpHM, reflux time Omepr: 129 (84–217) to 44 (6.1–128) Ran: 207 (66–306) to 58.4 (32–128)</td>
<td>Double blind RCT; 7 (22%) drop out; 6 month follow up. High relapse rate after treatment; 5/13 (38%) ranitidine and 7/12 (58%) omeprazole patients were still symptomatic, 2 required antireflux surgery</td>
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<td>Kato et al (1996)</td>
<td>13 cases (3–18 years) with oesophagitis and/or ulcer; failed cimetidine or famotidine. Omeprazole 0.6 mg/kg/day for 9 months; 5 without GI disease, 4 with ulcers treated with cimetidine or famotidine</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% Criteria for healing not clear (biopsy results not reported); No controls</td>
<td>No treatment for patients with H pylori; 7/12 (58%) relapsed</td>
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<td>Gunasekaran et al (1993)</td>
<td>15 children (0.8–17 years) with oesophagitis and failed H₂ blocker and prokinetic therapy; 4 with fundaplication</td>
<td>Case series</td>
<td>Clinical</td>
<td>Follow up 3 months: decreased symptoms 75% 6 months: decreased symptoms all</td>
<td>No controls; 8 neurologically impaired children and 1 with CF. Gastroscopy at 6 months only done on patients with endoscopic evidence of reflux at first follow up</td>
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<td>De Giacomo et al (1997)</td>
<td>10 children (25–109 months) with abnormal GOR and severe oesophagitis, failed prokinetic, H₂ blocker or antacid therapy</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>Alliet et al (1998)</td>
<td>12 children (2.9 ± 0.9 months); oesophagitis and failed cimetidine, positioning, cisapride, or Gaviscon therapy. Omeprazole 0.5 mg/kg/day for 6 weeks</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>Hassall et al (2000)</td>
<td>57 children [1–16 years] with erosive oesophagitis and pathologic acid reflux (pH &lt;4 for &gt;6% of the time). Treatment began at 0.7 mg/kg/day and increased by 0.7 mg/kg/day q 5–14 days to a max of 3.5 mg/kg/day if pathologic reflux was still present. Treatment continued for 3 months after healing dose was determined</td>
<td>Case series (prospective)</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>Karjoo et al (1995)</td>
<td>153 children (6–18 years) with 3 weeks of epigastric pain had OGD; 129 (84%) with oesophagitis were given high dose ranitidine (4 mg/kg/dose BID-TID for 4 weeks); 38 (30%) non-responsive to ranitidine were given omeprazole (20 mg/day) for 8 weeks</td>
<td>Case series (prospective)</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) Degree of oesophagitis on gastroscopy predictive of response to ranitidine (90% of patients with grade 1 respond). No long term follow up</td>
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Treatment. Six of the seven studies included patients who had failed other treatment modalities. Four of the five studies 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.

**Table 3**

<table>
<thead>
<tr>
<th>Citation</th>
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<tr>
<td>Stevens et al (2001)</td>
<td>Systematic review of 17 RCTs comparing sucrose to placebo</td>
<td>Systematic review (level 1a)</td>
<td>Behavioural (crying time, quality of suck), physiological (heart rate, respiratory rate, O₂ saturation), multidimensional behavioural pain scores</td>
<td>Significant reduction in behavioural and physiological indicators of pain and in multidimensional pain scores. E.g. weighted mean difference for pain scores pooled across 3 studies at 30 sec after heel prick: -1.64 (95% CI -2.47, -0.81) and at 60 sec -2.05 (95% CI -3.08, -1.02)</td>
<td>Patients studied ranged from 27 weeks to term babies. Doses used in studies were varied, ranging from 0.012 to 0.12g sucrose. Only one study looked at adverse effects. Ten studies did not completely double blinded as they used pacifiers as one of the experimental arms. Frequently studies did not report concealment of randomisation. Overall, however, all included studies were carefully planned and well designed</td>
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<td>Abad et al (2001)</td>
<td>51 term babies, &lt;4 days old (55 venepunctures) randomised to 2ml 24% sucrose, 2ml spring water, 1g EMLA or sucrose and EMLA</td>
<td>RCT (level 1b)</td>
<td>Crying time, heart rate, O₂ saturation, respiratory rate</td>
<td>Sucrose (compared with sterile water as placebo) significantly reduced crying time p&lt;0.001 and heart rate p=0.04. (No absolute figures for crying time or heart rate given)</td>
<td>Study excluded by Cochrane review as 4 babies were included twice as they received 2 venepunctures during study period. The venepunctures were separated by at least 24 hours and the babies were randomised to another arm</td>
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<tr>
<td>Blass et al (1991)</td>
<td>54 term babies, 28–54 hours old randomised to 2ml 12% sucrose or 2ml sterile water</td>
<td>RCT (level 1b)</td>
<td>Crying time during procedure and over 3 minutes following procedure</td>
<td>Sucrose with pacifier (compared with sterile water with pacifier) significantly reduced crying time during procedure (expressed as percentage of total procedure time) sucrose 42%, water 80%, p&lt;0.01</td>
<td>Study excluded by Cochrane review as the number of neonates in each experimental group not stated</td>
</tr>
<tr>
<td>Blass et al (1997)</td>
<td>72 neonates, birth weight 2976–3697g, 22–40 hours old randomised to 2ml of: sucrose, water, similac milk, Ross special formula, dilute fat, concentrated fat, lactose, lactose or protein</td>
<td>RCT (level 1b)</td>
<td>Crying time during procedure and over 3 minutes following procedure</td>
<td>Sucrose (compared with sterile water) significantly reduced crying time during procedure (expressed as percentage of total procedure time) sucrose 47%, water 92%, p&lt;0.015</td>
<td>As there were 9 experimental groups in this study there were only 8 subjects in each group</td>
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**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.
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 words: “sucrose” AND “pain” AND “neonate”.
Limits (in Medline): study type: randomised control trial; age: birth to 23 months; language: English.
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 preterm 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. Investigators also found that a repeated dose of sucrose is more effective than a single dose. 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.

▶ 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