

Towards evidence based medicine for paediatricians

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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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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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- 3 Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;123:A12–13.
- 4 Bergus GR, Randall CS, Sinift SD, et al. Does the structure of clinical questions affect the outcome of curbside consultations with specialty colleagues? *Arch Fam Med* 2000;9:541–7.
- 5 <http://cebmr2.ox.ac.uk/docs/levels.htm> 6
- 6 Sackett DL, Starus S, Richardson WS, et al. *Evidence-based medicine. How to practice and teach EBM*. San Diego: Harcourt-Brace, 2000.
- 7 Moyer VA, Elliott EJ, Davis RL, et al, eds. *Evidence based pediatrics and child health, Issue 1*. London: BMJ Books, 2000.

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? etc”).
- *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

Secondary searches—Cochrane, Clinical Evidence—none. Medline 1996–2001, using the OVID interface.

Table 1

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Daoud <i>et al</i> (1997)	67 children with BHS were randomised to either ferrous sulphate or placebo	RCT (level 1b)	Frequency of BHS per month after 16 weeks. Complete response (no attacks), partial response ($\geq 50\%$ reduction), minimal or no response ($< 50\%$ reduction)	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)	The baseline mean Hb in children who showed a response was 86 g/l compared to 106 g/l in those that responded poorly ($p=0.004$)
Mocan <i>et al</i> (1999)	91 children with breath holding spells. 63 with concomitant IDA	Case control (level 4)	Frequency of BHS over the 3 months study period. Complete response (no attacks), partial response ($\geq 50\%$ reduction), no response	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)	Only those children with BHS and IDA were treated with iron. The placebo group were those with BHS but normal Hb
Bhatia <i>et al</i> (1990)	50 children with BHS	Case series (level 4)	A reduction in frequency and severity of BHS following a course of iron which was continued until Hb > 11 g/dl	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	Failed to define improvement

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).

Daoud AS, Batieha A, Al-Sheyyab M, *et al*. Effectiveness of iron therapy on breath-holding spells. *J Pediatr* 1997;130:547–50.

Mocan H, Yildiran A, Orhan F, *et al*. Breath holding spells in 91 children and response to treatment with iron. *Arch Dis Child* 1999;81:261–2.

Bhatia MS, Singhal PK, Dhar NK, *et al*. Breath holding spells: an analysis of 50 cases. *Indian Pediatr* 1990;27:1073–9.

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

Pubmed: “treatment of gastroesophageal reflux in children”—limited to ages 0–18, English language, and human subjects. 1966–present: 1039 articles, seven relevant. See table 2.

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

Table 2

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Cucchiara <i>et al</i> (1993)	32 children (6 months to 13 years) with severe reflux oesophagitis and failed ranitidine and cisapride. Patients randomised to high dose ranitidine (20 mg/kg/day) or omeprazole (40 mg/day/1.73m ²) for 8 weeks	RCT	Clinical Oesophageal pH monitoring (OpHM) Gastroscopy (histology)	Both regimens effective. Decreased clinical score (p<0.01) Omep: 24 (15–33) to 9 (0–18) Ran: 19.5 (12–33) to 9 (6–12) Decreased OpHM reflux time Omep: 129 (84–217) to 44.6 (0.16–128) Ran: 207 (66–306) to 58.4 (32–128) Decreased histologic score (p<0.01) Omep: 8 (6–10) to 2(0–6) Ranit: 8 (8–10) to 2(2–6)	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
Kato <i>et al</i> (1996)	13 cases (3–18 years) with oesophagitis and/or ulcer; failed cimetidine or famotidine. Omeprazole 0.6 mg/kg/day 9 controls; 5 without GI disease, 4 with ulcers treated with cimetidine or famotidine	Case-control	Gastroscopy Gastric-pHM	Benefit in biopsy (healing rate): 2 weeks 46%; 4 weeks 85%; 6 weeks 92%; 8 weeks 92% Mean gastric pH Controls: 2.1 (1.8–2.5) Omep: 5.2 (3.0–6.6) (p=0.005) Cim/Fam: 3.1 (1.9–3.8) (p=0.05)	Criteria for healing not clear (biopsy results not reported); No controls No pretreatment pH studies; No treatment for patients with <i>H pylori</i> ; 7/12(58%) relapsed.
Gunasekaran <i>et al</i> (1993)	15 children (0.8–17 years) with oesophagitis and failed H ₂ blocker and prokinetic therapy; 4 with fundoplication Omeprazole (0.7–3.3 mg/kg/day) for 5.5–26 months. Dose titrated upward against 24° EpHM	Case series	Clinical Gastroscopy OpHM	Follow up:3 months: decreased symptoms 75% 6 months: decreased symptoms all 6 months: 9/15 had gastroscopy and all 9 improved Before treatment pH<4 for 11–88% of time. After treatment normal pH (<4 for < 6% of time)	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
De Giacomo <i>et al</i> (1997)	10 children (25–109 months) with abnormal GOR and severe oesophagitis, failed prokinetic, H ₂ blocker or antacid therapy	Case series	Clinical Gastroscopy Histology OpHM	Decreased symptoms all (p<0.05) Decreased score all No difference in histologic scores Decreased GOR (% , no., no. >5 min., and longest GOR)	No controls; 4 (40%) with significant comorbidities; 6 (60%) relapse after therapy; 3 required antireflux surgery
Alliet <i>et al</i> (1998)	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	Case series	Clinical Gastroscopy Biopsy OpHM during Rx	Decreased symptoms 10/12 (83%) 9 (75%) had completely normal mucosa; 3 (25%) improved 8 (67%) completely healed; 4 (33%) improved Decreased intragastric acidity (no p values)	No controls. One year follow up 83% asymptomatic
Hassall <i>et al</i> (2000)	57 children (1–16years) with erosive oesophagitis and pathologic acid reflux (pH <4 for >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	Case series (prospective)	Clinical Gastroscopy	Decreased symptoms: 53 (93%) Healed: 54 (98%). Median healing time 102 days	21 (37%) neurologically impaired; 7 (12%) repaired oesophageal atresia. No treatment for patients with <i>H pylori</i> No long term follow up
Karjoo <i>et al</i> (1995)	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	Case series (prospective)	Gastroscopy	91/129 (70%) responded to ranitidine; 38/129 (30%) non-responsive to ranitidine; 33/38 (87%) responded to omeprazole (p<0.05); 5 (4%) failed both treatments (3 had Nissen funduplications)	Degree of oesophagitis on gastroscopy predictive of response to ranitidine (90% of patients with grade 1 respond). No long term follow up

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.

Cucchiara S, Minella R, Iervolino C, *et al*. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. *Arch Dis Child* 1993;**69**:655–9.

Kato S, Ebina K, Fujii K, *et al*. Effect of omeprazole in the treatment of refractory acid-related diseases in childhood: endoscopic healing and twenty-four-hour intragastric acidity. *J Pediatr* 1996;**128**:415–21.

Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr* 1993;**123**:148–54.

De Giacomo C, Bowa P, Franceschi M, *et al*. Omeprazole for severe reflux esophagitis in children. *J Pediatr Gastroenterol Nutr* 1996;**128**:415–21.

Alliet P, Racs M, Bruneel E, *et al*. Omeprazole in infants with cimetidine-resistant peptic esophagitis. *J Pediatr* 1998;**132**:352–4.

Hassall E, Israel D, Shepherd R, *et al*. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. *J Pediatr* 2000;**137**:800–7.

Karjoo M, Kane R. Omeprazole treatment of children with peptic esophagitis refractory to ranitidine therapy. *Arch Pediatr Adolesc Med* 1995;**149**:267–71.

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.

Table 3

Citation	Study group	Study types (level of evidence)	Outcome	Key results	Comments
Stevens <i>et al</i> (2001)	Systematic review of 17 RCTs comparing sucrose to placebo	Systematic review (level 1a)	Behavioural (crying time, quality of suck), physiological (heart rate, respiratory rate, O ₂ saturation), multidimensional behavioural pain scores	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)	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 were 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
Abad <i>et al</i> (2001)	51 term babies, <4 days old (55 venepunctures) randomised to 2ml 24% sucrose, 2ml spring water, 1g EMLA or sucrose and EMLA	RCT (level 1b)	Crying time, heart rate, O ₂ saturation, respiratory rate	Sucrose (compared with sterile water as placebo) significantly reduced crying time p=0.001 and heart rate p=0.04. (No absolute figures for crying time or heart rate given)	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
Blass <i>et al</i> (1991)	54 term babies, 28–54 hours old randomised to 2ml 12% sucrose or 2ml sterile water	RCT (level 1b)	Crying time during procedure and over 3 minutes following procedure	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<0.01	Study excluded by Cochrane as the number of neonates in each experimental group not stated
Blass <i>et al</i> (1997)	72 neonates, birth weight 2976–3697g, 22–40 hours old randomised to 2ml of: sucrose, water, simlac milk, Ross special formula, dilute fat, concentrated fat, fat/lactose, lactose or protein	RCT (level 1b)	Crying time during procedure and over 3 minutes following procedure	Sucrose (compared with sterile water) significantly reduced crying time during procedure (expressed as percentage of total procedure time) sucrose 47%, water 92%, p<0.015	As there were 9 experimental groups in this study there were only 8 subjects in each group

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.⁶⁻⁸ Investigators also found that a repeated dose of sucrose is more effective than a single dose.⁵

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.¹

► 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**.

Abad F, Diaz-Gomez NM, Domenech E, *et al*. Oral sucrose compares favourably with lidocaine-prilocaine cream for pain relief during venepuncture in neonates. *Acta Paediatr*. 2001;**90**:160–5.

Blass EM, Hoffmeyer LB. Sucrose as an analgesic for newborn infants. *Pediatrics* 1991;**87**:215–18.

Blass EM. Milk-induced hypoalgesia in human newborns. *Pediatrics* 1997;**99**:825–9.

Johnston CC, Stremmler R, Horton L, *et al*. Effect of repeated doses of sucrose during heel stick procedure in preterm neonates. *Biol Neonate* 1999;**75**:160–6.

Abad F, Diaz NM, Domenech E, *et al*. Oral sweet solution reduces pain-related behaviour in preterm infants. *Acta Paediatr* 1996;**85**:854–8.

Ramenghi LA, Wood CM, Griffith GC, *et al*. Reduction of pain response in premature infants using intraoral sucrose. *Arch Dis Child Fetal Neonatal Ed* 1996;**74**: F126–8.

Haouari N, Wood C, Griffiths G, *et al*. The analgesic effect of sucrose in full term infants: a randomised controlled trial. *BMJ* 1995;**310**:1498–500.