

# 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.<sup>1</sup> *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*.<sup>2</sup>

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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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,<sup>3</sup> and gaining answers.<sup>4</sup>) 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.<sup>5</sup> 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<sup>6</sup> and Moyer<sup>7</sup> 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.

- ▶ Albumin infusion in hypoalbuminaemic children with oncological disease
- ▶ Magnesium sulphate in paediatric status asthmaticus
- ▶ Chiropractic in infantile colic

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## REFERENCES

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- 5 <http://cebim.jr2.ox.ac.uk/docs/levels.htm>
- 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.

## The good, the bad, and the unhelpful

How can we quantify the likely benefits and harms of treatments? For each treatment we have, there is a series of outcomes; we can calculate the "number needed to treat" (NNT) for good outcomes and "number needed to harm" (NNH) for adverse events. For antibiotic treatment of otitis media, there is an NNT -7 to prevent pain at 48 hours, and an NNH -7 to produce a rash, vomiting, or diarrhoea.

Does the simple equivalence of good and bad outcomes mean that the treatment has no overall effect? To make a balanced assessment you should take into account the severity of the outcome. (If the treatment had the effect of preventing death in 1 of 50 cases, but produced vomiting in 1 of 10 cases, is this a treatment which is five times as bad as good?) The weighing of one outcome against another can more formally assess this. The assessment is the "likelihood of being helped over harmed" or LBHH:

LBHH = NNT/(NNH × how much worse bad outcome is over good)

For example, if a parent believed "vomiting, rash, or diarrhoea" is half as bad as "pain at 48 hours", the LBHH would be  $7/(7 \times 0.5) = 2$ . (Antibiotics for otitis media are considered twice as good as bad.) This approach can be used to personalise the evidence to the patient, and make more transparent the process of evidence based decision making.

## Does giving albumin infusion in hypoalbuminaemic children with oncological disease affect colloid osmotic pressure and outcome?<sup>1</sup>

### Report by

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A 16 month old boy with stage IV neuroblastoma and hypoalbuminaemia presented with a left sided haemorrhagic pleural effusion. He subsequently developed generalised oedema. You wonder if there was a role of albumin infusion in correcting hypoalbuminaemia and colloid osmotic pressure (COP), in order to treat the extravasation of fluid into tissue spaces.

Table 1

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Mahlon and Navickis (2001)	55 randomised controlled trials comparing albumin therapy with other interventions	Systematic review (level 1a)	Relative risk of death	Pooled relative risk for death was 1.11 (95% CI 0.95 to 1.28). Relative risk for death in hypoalbuminaemia group was 1.59 (95% CI 0.91 to 2.78). Overall, no effect of albumin on mortality detected	Relative risk was lower in trials with blinding, mortality as end point, no crossover, and 100 or more patients. Only 5 trials dealt with patients with hypoalbuminaemia
Alderson <i>et al</i> (2001)	30 randomised controlled trials comparing albumin with other interventions in critically ill patients	Systematic review (level 1a)	Mortality	For hypoalbuminaemia relative risk of death was 1.69 (95% CI 1.07 to 2.67). Pooled relative risk of death with albumin was 1.68 (95% CI 1.26 to 2.23). The risk of death in the albumin treated group was higher than in the comparison group	Large peer response ( <i>BMJ</i> 1998; <b>317</b> :882, 1999; <b>318</b> :464, 1214). Small trial bias, lack of enough trials in the paediatric population and concerns over homogeneity through the trials
Blunt <i>et al</i> (1998)	145 survivors and non-survivors of prolonged critical illness	Retrospective review of practice (level 4)	COP and mortality	Non-survivors had significantly lower mean serum albumin compared with survivors; $p < 0.05$ . Albumin only contributed to 17% of the COP in critically ill patients. There was no relation between death and COP	Adult pattern disease: one half of this population were postoperative patients, e.g. aortic aneurysm, gastrointestinal and renal patients
Grundmann and Heistermann (1985)	220 patients on adult ITU randomised to receive albumin when COP fell $< 24$ cm H <sub>2</sub> O (group 1) or COP $< 29$ cm H <sub>2</sub> O (group 2)	Prospective randomised controlled trial (level 1b)	Postoperative complications, COP, duration of intensive care and mortality	Albumin replacement did not influence the final outcome. The 95% CI of risk difference for mortality includes zero ( $-5.4\%$ , $-16.6$ to $5.8\%$ ). The absolute risk increase of lower COP ( $< 20$ cm H <sub>2</sub> O) for mortality was 50.5% (95% CI 20.5 to 80.5%)	Both groups received albumin. All patients were postoperative

### Structured clinical question

In critically ill children with low serum albumin [patient group] does giving albumin infusion [intervention] improve COP and hence morbidity and mortality [outcome]?

### Search strategy and outcome

Secondary sources—Cochrane Library (Issue 4, 2000): “hypoalbuminaemia”, seven systematic reviews (one relevant). PubMed clinical queries; LIMIT to English: “albumin” AND “critical illness”—159 references (one meta-analysis of 55 studies, four of which dealt with hypoalbuminaemia); “colloid osmotic pressure” AND “critical illness”—four references (one relevant to question); “hypoalbuminaemia” AND “critical illness”—six references (one relevant to question). See table 1.

### Commentary

There is a paucity of data in children. However, in critically ill adults a decrease in serum albumin is associated with increased morbidity and mortality. This may represent a disease related alteration in hepatic synthetic function. Albumin contributes up to 80% of COP in healthy subjects; however, its contribution towards COP is only 17% in critically ill individuals (Blunt *et al*). In adults, the studies suggest that albumin administration has no effect on mortality. In addition, its contribution towards COP is questionable. In fact, there appears to be no significant difference in COP of survivors compared with non-survivors of critical illness. Taken together, this information suggests that low serum albumin may merely be a surrogate marker of disease severity rather than an indicator of low COP. Hence, when treating patients with hypoalbuminaemia, efforts must be focused on correcting the underlying disorder, rather than reversal of hypoalbuminaemia; or, alternatively, on measuring COP directly. There are no such studies in children, but in the systematic reviews the relation between mortality and albumin administration was similar to that described in adults.

We therefore speculate that in children with protracted or critical illness, such as seen in oncological or life threatening

disease, the adult relation between albumin, COP, and outcome may also hold. However, this idea should be tested by prospective biochemical study.

### ► CLINICAL BOTTOM LINE

- Little published research addresses the question of albumin use in oncological hypoalbuminaemia in children.
- Critically ill adults with hypoalbuminaemia do not have better outcomes when treated with albumin.

**Mahlon MW**, Navickis RJ. Patient survival after human albumin administration. *Ann Intern Med* 2001;**135**:149–64.

**The Albumin Reviewers** (Alderson P, Bunn F, Lefebvre C, *et al*). Human albumin solution for resuscitation and volume expansion in critically ill patients. (Cochrane Review). In *The Cochrane Library*, Issue 3. Oxford: Update Software, 2001.

**Blunt MC**, Nicholson JP, Park GR. Serum albumin and colloid oncotic pressure in survivors and nonsurvivors of prolonged critical illness. *Anaesthesia* 1998;**53**:755–61.

**Grundmann R**, Heistermann S. Postoperative albumin infusion therapy based on colloid osmotic pressure. *Arch Surg* 1985;**120**:911–15.

## Does magnesium sulphate have a role in the management of paediatric status asthmaticus?

Report by Barry Markovitz, Associate Professor of Anesthesiology and Pediatrics and Co-Editor, PedsCCM Evidence-based Journal Club at PedsCCM.org, Washington University School of Medicine, St Louis Children's Hospital, St Louis MO, USA

Jimmy was in the emergency department (ED) with his third severe asthma attack of the winter. He could tell he was going to be admitted ... again. He was not improving much after one hour on continuous nebulised albuterol and intravenous steroids. The new paediatric registrar was running around asking for the magnesium. The senior consultant looked at him like he was a misplaced obstetrician. What evidence did he have to suggest magnesium might make Jimmy better and prevent admission?

### Structured clinical question

In children with status asthmaticus [patient] does acute administration of intravenous magnesium sulphate [intervention] reduce hospital admission rate [outcome]?

### Search strategy and outcome

Cochrane Database of Systematic Reviews—none with children (1). Medline—“magnesium” AND “asthma” AND “child” AND [(double and blind) or placebo]—four pertinent trials in 18 hits. One additional meta-analysis was identified; hospital admission rate was not assessed as an outcome (2). See table 2.

### Commentary

Three of these four studies of intravenous MgSO<sub>4</sub> in paediatric ED patients with moderate–severe status asthmaticus showed significant reduction in hospitalisation rates compared to controls. (A formal meta-analysis of these trials would give a better quality answer than to simply add up study numbers.) These patients had all already been treated with maximal inhaled β agonist therapy and corticosteroids. The rough similarity of the asthma response rate (ARR) in the three positive trials suggests a real and clinically significant improvement in an obvious clinical endpoint—hospitalisation. MgSO<sub>4</sub> is easy to administer, can be used in conjunction with other therapies, and appears to show a clinical effect within one to two hours.

The Cochrane review combines adults and children, was performed before two of the studies (the Scarfone and 2nd Ciarallo papers) appeared, and did not separate out children in a subgroup analysis in terms of hospitalisation rates (Rowe *et al*, 2000). The other systematic review (Alter *et al*, 2000) did not evaluate hospital admission as an outcome measure. Though difficult to compare severity of patients across studies, all patients were “moderately to severely” affected and very likely to require hospitalisation. Furthermore, given the low cost and lack of any side effects noted across the studies (it will of course take thousands of patients studied to confidently conclude a drug is “safe”), intravenous magnesium may be indicated in paediatric refractory status asthmaticus. A formal systematic review of these studies is needed.

### CLINICAL BOTTOM LINE

- Magnesium sulphate may reduce hospitalisation rates of paediatric patients with severe status asthmaticus (NNT ~3).
- The most severely affected patients stand to benefit the most; MgSO<sub>4</sub> should be considered in refractory patients with impending respiratory failure.

Rowe BH, Bretzlaff JA, Bourdon C, *et al*. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev* 2000;2:CD001490.

Alter HJ, Koepsell TD, Hilty WM. Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. *Ann Emerg Med* 2000;36:191–7.

Devi PR, Kumar L, Singhi SC, *et al*. Intravenous magnesium sulfate in acute severe asthma not responding to conventional therapy. *Indian Pediatr* 1997;34:389–97.

Scarfone RJ, Loiselle JM, Joffe MD, *et al*. A randomized trial of magnesium in the emergency department treatment of children with asthma. *Ann Emerg Med* 2000;36:572–8.

Ciarallo L, Sauer AH, Shannon MW. Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996;129:809–14.

Ciarallo L, Brousseau D, Reinert S. Higher-dose intravenous magnesium therapy for children with moderate to severe acute asthma. *Arch Pediatr Adolesc Med* 2000;154:979–83.

## Is chiropractic an effective treatment in infantile colic?

### Report by

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Mrs A presents with her 6 week old baby, complaining of his excessive and uncontrollable crying behaviour, particularly in the evening and at night. The child is otherwise healthy, thriving, and has a normal weight gain. Following questions regarding the pattern of crying, and associated signs, it is apparent that the child is exhibiting typical colic behaviour. There are clear signs that the continual and excessive crying behaviour is impairing the mother–child relationship, and you consider the child might be at increased risk of harm (or neglect). In discussing the treatment options, Mrs A tells you that her chiropractor has offered to treat her baby for the excessive crying behaviour. She herself has been

**Table 2**

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Devi <i>et al</i> (1997)	47 children in ED with severe status asthmaticus	RCT (level 1b)	Admission to hospital	ARR 0.34 (95% CI 0.07 to 0.61); NNT 3 (95% CI 2 to 14)	0.2 cc/kg 50% MgSO <sub>4</sub> given
Scarfone <i>et al</i> (2000)	54 children in ED with moderate status asthmaticus	RCT (level 1b)	Admission to hospital	ARR 0.07 (95% CI –0.2 to 0.34), NNT 14 (95% CI 3 to 8; NNH 8 to 5)	75 mg/kg MgSO <sub>4</sub> (max 2.5 g)
Ciarallo <i>et al</i> (1996)	31 children in ED with moderate to severe status asthmaticus	RCT (level 1b)	Admission to hospital	ARR 0.27 (95% CI 0.05 to 0.49), NNT 4 (95% CI 2 to 19)	25 mg/kg MgSO <sub>4</sub> (max 2 g)
Ciarallo <i>et al</i> (2000)	30 children in ED with moderate to severe status asthmaticus	RCT (level 1b)	Admission to hospital	ARR 0.5 (95% CI 0.24 to 0.76), NNT 2 (95% CI 1 to 4)	40 mg/kg MgSO <sub>4</sub> (max 2 g)

Table 3

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Klougart <i>et al</i> (1989)	316 otherwise healthy infants (age 2–16 weeks) with symptoms of colic according to well defined criteria, all treated with chiropractic spinal manipulation. Primary evaluation after two weeks of treatment (average of 3 treatment visits). Number of dropouts = 17	Prospective single cohort observational study (level 2b)	Daily hours of crying using diary completed by parents	Mean no. of daily hours crying over 2 days before treatment (retrospective estimate): 5.2. At day 1: 2.5, and at day 14: 0.65 (74% reduction). Unclear whether infants had been treated on day 1	Lack of blinding introduces considerable bias. Lack of randomisation and a control group prevents estimates of a placebo effect or natural course of the condition, which is known to improve with age. The study is however important because of the large number of infants recruited
			Symptom improvement score estimated by parents	At day 14; 6% of sample no change or worse, 34% improved, 60% stopped colic symptoms	
Mercer and Nook (1999)	30 infants (0–8 weeks) suffering from infantile colic diagnosed by a paediatrician (criteria unclear). 15 infants treated by chiropractic spinal manipulation (experimental); 15 infants treated with a non-functional, de-tuned ultrasound machine (placebo). In both groups, a maximum of 6 treatments over two weeks. No information given on dropouts	RCT (level 1b) Single blinded study. Randomisation unclear	Subjective response to treatment by parents before treatment and at each subsequent consultation. Outcomes not defined	Statistically significant difference (no data given) in response to treatment between 2 groups (assumed beneficial in experimental group). Complete resolution of symptoms in 93% of infants in (assumed) experimental group. No comparative data for placebo group	This study was reported in abstract form. The small sample group without well defined inclusion data and the lack of detail in methodology and recorded data seriously undermines the contribution of this study to the evidence base. Nevertheless, it is reported for completeness, and does support the suggestion of a beneficial effect of chiropractic
Wiberg <i>et al</i> (1999)	50 objectively healthy infants (age 2–10 weeks) with well defined colic. 25 treated with chiropractic spinal manipulation for two weeks (mean 3.8 treatments) and 16 with dimethicone for two weeks (9 dropouts)	RCT (level 1b) Single blinded study. Method of randomisation unclear	Daily hours of crying using diary (completed by parents)	At 8–11 days, mean change in no. of hours crying: –1.0 (SE 0.4) dimethicone; –2.7 (0.3) spinal manipulation (p=0.004)	Parents reporting outcome knew the intervention. Dimethicone has been shown to be no better than placebo treatments. No follow up period after treatment period so unsure whether observed effect is maintained
Olafsdottir <i>et al</i> (2001)	100 colicky infants (age 3–9 weeks) meeting strict entry criteria. 50 treated with chiropractic spinal manipulation for 3 visits (over 8 days) and 50 given placebo treatment (holding). (9 infants excluded (failure to meet entry criteria) and 5 drop outs leaving 86 completing trial)	RCT (level 1b) Double blinded study. Randomisation by sealed envelopes	Daily hours of crying using diary (completed by parents)	At third (last) visit (day 8), mean no. of hours crying: 3.1 (SD 2.7) spinal manipulation; 3.1 (SD 2.7) placebo (p=0.982)	No results given for follow up period after treatment finished. No CI or RR given in spite of reference to them in the methods
			Symptom improvement score 8–14 days after last visit (completed by parents)	No difference in symptom scores between spinal manipulation and placebo (p=0.743). NNT = 10 (95% CI 3 to ∞); NNH (95%CI 9 to ∞)	No results given for improvement after visits 1 and 2

treated by this chiropractor in the past for back pain, and it is obvious she has considerable confidence in him. She asks your advice.

### Structured clinical question

In an otherwise healthy 6 week old infant with typical colicky pain [patient], is chiropractic [intervention] effective in reducing the severity of the colic, or the length of time spent crying [outcome]?

### Search strategy and outcome

Medline: “colic” AND “chiropractic” AND filter “therapy”—three articles; ((colic AND chiropractic) AND (randomized controlled trial [PTYP] OR drug therapy [SH] OR therapeutic use [SH:NOEXP] OR random\* [WORD]))—two articles, (both RCTs). Hand searching—abstract (Mercer and Nook). See table 3.

### Commentary

The early prospective study is the first documented evidence to indicate a possible beneficial effect of chiropractic intervention in colic, and as such highlights the need for future RCTs. The RCT reported by Mercer and Nook is only published in abstract form, and the lack of detail prevents scrutiny of its methodology and data analysis. It is therefore not included in the best evidence available for the effectiveness of chiropractic for colic.

Both RCTs (Wiberg *et al* and Olafsdottir *et al*) were comparable in design and of good quality. The major difference was in the blinding of parents who completed the crying diary (and the symptom improvement score) and therefore in the reduction of parents’ bias. This strengthens the trial by Olafsdottir *et al*, and their conclusion that chiropractic offers no greater efficacy in treating infantile colic than placebo. On the other hand, the positive effects of spinal manipulation reported by Wiberg *et al* are almost certainly not as beneficial as they would have been had an intention to treat analysis been carried

out. All nine dropouts in the dimethicone group were as a result of a worsening of symptoms (and not parents' bias against medication). There were no dropouts in the spinal manipulation group. The first study is a study of effectiveness—it is pragmatic. Parents taking their child to a chiropractor clearly report a significant improvement. By eliminating parental bias, the second study is an efficacy study of chiropractic intervention. Chiropractic itself does not appear to be efficacious. An alternative explanation for these disparate results is postulated by Grunnet-Nilsson and Wiberg who hypothesise a dose-response phenomenon. In the trial by Olafsdottir *et al*, a treatment protocol of a maximum of three sessions of spinal manipulation was used over eight days, whereas the study by Wiberg *et al* relied on the clinical judgement of the chiropractor. All infants received three to five sessions of chiropractic over a 14 day period (64% greater than three). Again this reflects the pragmatic nature of the study by Wiberg *et al*, and the investigation of effectiveness as opposed to efficacy of a treatment intervention.

#### ► CLINICAL BOTTOM LINE

- The evidence suggests that chiropractic has no benefit over placebo in the treatment of infantile colic. However, there is

good evidence that taking a colicky infant to a chiropractor will result in fewer reported hours of colic by the parents.

- In this clinical scenario where the family is under significant strain, where the infant may be at risk of harm and possible long term repercussions, where there are limited alternative effective interventions, and where the mother has confidence in a chiropractor from other experiences, the advice is to seek chiropractic treatment.

**Klougart N**, Nilsson N, Jacobsen J. Infantile colic treated by chiropractors: a prospective study of 316 cases. *J Manipulative Physiol Ther* 1989;12:281–8.

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**Grunnet-Nilsson N**, Wiberg JMM. Infantile colic and chiropractic spinal manipulation [letter]. *Arch Dis Child* 2001;85:268.

## ARCHIVIST .....

### Fame, power, and Asperger's syndrome

Do all emotionally cold, single minded, autocratic odd bods suffer from Asperger's syndrome? A professor of child psychiatry at Trinity College, Dublin (Michael Fitzgerald. *Journal of Medical Biography* 2001;9:231–5) has described these personality traits in Ireland's first president, Eamon De Valera, and suggested this diagnosis.

Professor Fitzgerald lists the six commonly quoted criteria for the diagnosis of Asperger's syndrome (severe impairments in reciprocal social interaction, all-absorbing narrow interests, imposition of routines on self and others, non-verbal communication problems, speech and language problems, and motor clumsiness). (The last two are not included in the fourth edition of the American Psychiatric Association Diagnostic and Statistical Manual (DSM-IV).) He goes on to provide an extremely unflattering picture of President De Valera based in large part on two biographies. Descriptions of the president include expressions such as odd, baffling, arrogant, an outsider, lacking in social graces, tactless, aloof, lacking empathy, and humourless. He is said to have been extremely autocratic and sure of the rightness of his own views. He was obsessed by Irish nationalism and absorbed by mathematics. (The latter interest led to his election as a Fellow of the Royal Society in 1968.) (DSM-IV refers to "preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus"; whether intense Irish nationalism or an interest in mathematics comes into this category seems at least debatable.) He was a stickler for routine, had a liking for uniforms, and involved himself in the minutiae of government. As a public speaker he was said to be verbose, pedantic, repetitious, and condescending. Professor Fitzgerald concludes that De Valera met the DSM-IV criteria for Asperger's syndrome.

We have all met aloof, difficult, cold fish who are "never wrong". Do they have Asperger's syndrome? Does it help to say that they do? If you saw Maureen Lipman playing the part of the play agent Peggy Ramsay in Alan Plater's play *Peggy for You* you will have seen a very funny portrait of an eccentric, obsessional, infuriating, but seemingly loveable character who had many of the features of Asperger's syndrome. Making that diagnosis at the theatre made me feel clever and perhaps slightly smug but was it really much better than most people's diagnosis of extreme eccentricity?