ARCHIMEDES

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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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. In doing this, we are adapting a format which has been successfully developed by Kevin Macaway-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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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 aid in focusing the mind, assisting searching,[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 Sackett[5] and Moyer[6] 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.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- Is two thumb or two finger CPR in infants more effective?
- Does oral diazepam prevent febrile convulsions?

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.

- Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms
- Is an intravenous fluid bolus of albumin or normal saline beneficial in the treatment of metabolic acidosis in a normovolaemic newborn?
- How safe is ibuprofen in febrile asthmatic children?

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Putting evidence into practice: part 2

How do your remember what you read in a paper? How do you call to mind that reference about petechiae and vomiting that means you don't have to stick this perfectly well 8 year old needle-phobic? Capturing the outputs of your critical appraisals so you can retrieve them is easier if you formally record them in some way. These records have been described by lots of different people in lots of different ways. They are called a number of things, mostly with punishingly painful acronyms attached. Hence you get ''critically appraised topics'' (CATs—probably the most generic phrase), ''best evidence topics'' (BETs), or ''patient orientated evidence that really matters'' (POEMs) depending on where you live or work. The topics you read here in Archimedes are printed as BETs, with fuller individual CATs on the *ADC* website. A template you can fill in with your own questions is also available on the website, along with Instructions to Authors.

The underlying principles of all these different records are fairly similar. They have a *headline* which describes either the question under consideration or a compact form of the answer. They have the *question* that triggered the CAT to be created. They detail the *study methodology* and comment on strengths and weaknesses, and relay the relevant *results*. They may have further comments, but nearly all will have a summary of the *clinical bottom lines*.

Once you've created your summaries, you still need to keep them accessible. Placing them all (with copies of Archimedes) in a big red folder might seem a bit cheesy, but it's been shown to be an effective way of getting clinical questions answered quickly.[1] It also doesn't rely on your hospital computer working, and can be safely accessed while drinking coffee. It has the benefit of having instant feedback too—with the aid of a pencil or pen, comments can be added to the margins without difficulty. The more technologically minded might want to put your own on a website. Many widely used word processing programmes will allow you to save your version of an evidence summary as web (html) pages. (From there, getting them onto a website is then a case of finding someone with a bit of IT knowledge.) Developing the technological idea further, a PDA (handheld computer) version could be made by those with adequate skills.

Of course, the next logical step when you've worked with your colleagues to produce a high quality summary of the evidence related to a clinically important question is to submit it to Archimedes. You too could be the next proud provider of information which makes clinical paediatrics more evidence based.

Reference

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Additional information on each of the topics is available on the *ADC* website (www.archdischild.com/supplemental)

Short stature and the probability of coeliac disease, in the absence of gastrointestinal symptoms

Report by

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An 8 year old girl is referred to the paediatrician because of her stunted growth. Her height SDS is −2.3 (≈1st centile); her weight for height ratio is +0.9 SDS (≈80th centile). At the age of 3 years, her height SDS was +0.3 (≈60th centile). Her weight for height ratio had not changed considerably. At the age of 4–5 years, she had several episodes of constipation and anaemia. There were no other complaints. A diagnostic work-up was performed: IgA anti-endomysium (IgA EmA) antibodies were positive. A small intestinal biopsy (gold standard) showed total villous atrophy, consistent with coeliac disease. During follow up, she fulfilled the ESPGAN criteria for coeliac disease (finding of characteristic small bowel mucosa abnormalities in a small bowel biopsy, and clinical remission when placed on a gluten-free diet).

Structured clinical question

What is the prevalence of coeliac disease [outcome] in children with short stature and no gastrointestinal symptoms [patients]?

Search strategy and outcome

Pubmed—(body height AND (short OR little OR small OR abnormal) OR short stature OR dwarfism) OR failure to thrive AND coeliac disease (limited by: Ages: All child 0–18 year, Language: English);120 references of which 11 relevant and of sufficient quality (see table 1).

Embase—same search strategy; no additional relevant references.

Cochrane database—same search strategy; none relevant.

The way study groups were selected varied. Articles with the least selective study groups are reported higher in the table than studies with a more selective study group.

Commentary

Growth retardation in childhood may be one of the earliest signs of an underlying disease, such as coeliac disease. In the Netherlands, the growth of nearly every child is monitored. When growth is retarded, the child is referred to secondary health care. After referral it has been advised to perform a diagnostic work-up containing routine laboratory tests to search for diagnostic clues for, among others, coeliac disease. The tests presently used for coeliac disease are IgA EmA and IgA antitissue transglutaminase antibodies. The total immunoglobulin A count is determined as well, because coeliac disease is associated with IgA deficiency. It was questioned if diagnostic investigations for coeliac disease should be performed in all children with short stature, even without gastrointestinal complaints.

Studies 1–5 were based on study groups, in which no preliminary (endocrine) work-up to exclude other causes for short stature had been performed. The proportion of coeliac disease in children with short stature and no gastrointestinal symptoms in these studies ranged from 1.7% to 8.3%. When a group of children was studied, in which endocrine causes for short stature had been excluded (studies 6–11), the proportion of coeliac disease increased to a range of 18.6–59.1%. The characteristics of the preliminary work-up used in study 12 were not described.

The wide range of these percentages is probably mainly caused by the different methods of selecting the patients. The true variation in prevalence of coeliac disease throughout the world appears to be limited.[13]

Screening for coeliac disease in the general population shows a prevalence of 1:300 to 1:100. About 50% of these children are completely symptomless.[13] In two British population based studies on short stature,[14 15] where coeliac disease was not specifically investigated, the prevalence of coeliac disease was 2:180 (one patient was already known with coeliac disease) and 0:149 respectively. In children with short stature and no gastrointestinal symptoms investigated for coeliac disease, the prevalence increases to 2–8%. When other (endocrine) causes for short stature are excluded, the prevalence might rise to even 59%.

CLINICAL BOTTOM LINE

- In 2–8% of children with short stature and no gastrointestinal symptoms, coeliac disease may be the underlying cause.
- Excluding other causes for short stature increases the risk of having coeliac disease by 19–59%.
- Children with short stature should be evaluated for coeliac disease.

Acknowledgements

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Table 1 Relation of short stature and coeliac disease

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Knudtzon *et al* (1991), Norway[1]	168 children (50 girls; 93 boys; age 0.5–17.2 years) with short stature without significant abdominal symptoms	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	2.9% (5/168) of the children with short stature were diagnosed as having coeliac disease	''Short stature'' was not defined Results are not internally consistent Diagnosis was not based on ESPGAN-criteria
Stenhammer *et al* (1986), Sweden[2]	87 children (32 girls, 55 boys; age 1.0–16.5 years) with short stature (height more than 2SD below the mean for age and sex) and no gastrointestinal symptoms, signs of systemic disease or malabsorption	Prospective cohort study (level 1b)	Proportion of coeliac disease in the study group	5% (4/87) children with short stature were diagnosed as having coeliac disease There is an overrepresentation of coeliac disease among short children admitted to hospital for examination	Diagnosis was made based on ESPGAN criteria Gold standard was applied to all children Results are not fully described
Cacciari *et al* (1985), Italy[3]	108 patients (30 girls, 78 boys; age 2.8–16.7 years) with short stature (height below third centile) and no gastrointestinal symptoms	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in study group	8.3% (9/108) patients with short stature were diagnosed as having coeliac disease	Gold standard was applied to all patients Diagnosis of coeliac disease was not according to ESPGAN criteria Possible overlap in patients in the two studies of Cacciari?
Cacciari *et al* (1983), Italy[4]	60 children (21 girls, 39 boys) with short stature (height below third centile) and no gastrointestinal symptoms	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in study group	8.3% (5/60) patients with short stature were diagnosed as having coeliac disease	Gold standard applied to all patients Diagnosis of coeliac disease was not according to ESPGAN criteria
Rossi *et al* (1993), USA[5]	117 children (age: 2–17 years) with height more than 2SD below the mean for age. Of these children, 57 were diagnosed with GH deficiency. All children were clinically and chemically euthyroid	Prospective cohort study (level 2b)	Proportion of coeliac disease in a group of children with short stature	1.7% (2/117) of children with short stature had biopsy proven coeliac disease There is an association between idiopathic short stature and coeliac disease	Basic data are not adequately described (no sex differentiation) Gold standard was not applied to all patients Diagnosis of coeliac disease was not according to ESPGAN criteria
Bonamico *et al* (1992), Italy[7]	49 children (27 girls, 22 boys; mean age 112 months (SD: 39)) with short stature (height below the third centile) and no gastrointestinal symptoms. None of the 49 patients showed somatic, cardiac, renal or chromosomal disorders	Prospective cohort study (level 1b)	Proportion of coeliac disease in the study group	59.1% (29/49) children with short stature were diagnosed as having coeliac disease	Gold standard was applied to all patients Diagnosis of coeliac disease was made according to ESPGAN criteria
Groll *et al* (1980), UK[8]	34 children (16 girls, 18 boys; age 2.5–17.0 years) with short stature (more than 2SD below the mean for age) and no gastrointestinal symptoms. There were no dysmorphic features, and endocrine investigations were normal	Prospective cohort study (level 1b/2b)	Proportion of coeliac disease in the study group	21% (8/34) children with short stature were diagnosed as having coeliac disease	Diagnosis was not according to ESPGAN criteria
Rosenbach *et al* (1986), Israel[9]	23 children (12 girls, 11 boys; age 6–16 years) below third centile for age and a bone age delay of at least 25%. Extensive preliminary work up (including hypothalamic, pituitary, adrenal, and gonadal functions, sweat test, stool examination for ova and parasites) was found to be negative	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	48.7% (11/23) of the patients with short stature were diagnosed as having coeliac disease	Gold standard was applied to all patients Diagnosis was not according to the ESPGAN criteria
de Lecea *et al* (1996), Spain[10]	118 children (49 girls, 69 boys; age 11 months to 14 years), with height less than third centile for age. Preliminary work up (absorption, hormonal and genetic studies, sweat test, *x* ray for bone age, serum IgA AGA) was performed	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	18.6% (22/118) of children with short stature had biopsy proven coeliac disease	Results were not presented. Numbers do not add up properly. Gold standard was not applied to all children. Diagnosis was not according to ESPGAN criteria Basic data were not adequately described

Table 1 Continued

Citation, country	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Altuntas *et al* (1998), Turkey[11]	47 patients (18 girls, 29 boys; age 4–16 years) of short stature (below third centile for height) without gastrointestinal tract symptoms or endocrinological, cardiac, renal or chromosomal disorders. There were no symptoms associated with coeliac disease or signs of cows' milk allergy	Cross-sectional study (level 1b/2b)	Proportion of coeliac disease in the study group	55.3% (26/47) of the short children had biopsy proven coeliac disease	All children were biopsied Results are not presented clearly; the reader cannot make his own conclusions Diagnosis of coeliac disease was not according to ESPGAN criteria
Tumer *et al* (2001), Turkey[12]	84 children (46 girls, 38 boys; age 16 months – 14 years) with height less than third centile for age; preliminary work-up to evaluate other causes of short stature was found to be negative	Prospective cohort study (level 2b)	Proportion of coeliac disease in the study group	Proportion of coeliac disease was found to be 8.3% (7/84) There is an association between coeliac disease and idiopathic short stature	The IgA EmA test was not verified by a gold standard test (biopsy) in all patients Diagnosis of coeliac disease was not according to ESPGAN criteria

Is an intravenous fluid bolus of albumin or normal saline beneficial in the treatment of metabolic acidosis in a normovolaemic newborn?

Report by
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At the age of 4 hours, a tachypnoeic, well hydrated, well perfused, and normotensive 34 week preterm neonate develops a metabolic acidosis (arterial pH 7.25, base deficit minus 10 mmol/l). There was no history of perinatal blood loss or sepsis risk factors. No resuscitation was required at birth, and the cord blood pH was 7.3. According to departmental protocol, volume expansion with an intravenous bolus of 10–20 ml/kg of normal saline or 4.5% albumin is advised. You wonder as to the value of this volume expansion.

Structured clinical question

In the absence of asphyxia or hypovolaemia in a newborn infant with metabolic acidosis [patient] does an intravenous bolus of normal saline or albumin [intervention] improve the following [outcomes]: pH, base deficit, mortality, morbidity, length of hospital stay, neurodevelopmental disability?

The outcomes were defined as follows:

- Mortality = neonatal mortality and mortality to discharge.
- Morbidity = peri/intraventricular haemorrhage of any grade, periventricular leucomalacia, patent ductus arteriosus, renal impairment (raised serum creatinine, oliguria), air leak, chronic lung disease (at 28 postnatal days or near term postmenstrual age), necrotising enterocolitis, or retinopathy of prematurity of any grade.
- Neurodevelopmental disability = neurological abnormality including cerebral palsy, developmental delay, or sensory impairment.

Search strategy and outcome

Exclusion criteria: trials including infants with clinically suspected poor perfusion (e.g. low blood pressure, poor cutaneous perfusion) or trials including unselected newborn infants (not known to have metabolic acidosis).

Secondary sources—Cochrane Library (Issue 3, 2003): one protocol—two control trials in CENTRAL, of which one was relevant.

PubMed (1975–2003): search words—(''metabolic acidosis'') AND (''therapy'' OR ''fluid'' OR ''albumin'' OR ''colloid'' OR ''sodium chloride'') using Clinical Queries methodological filters category (therapy, prognosis) and emphasis (sensitivity, specificity). Limits—Newborn. Search outcome: 87 papers, of which two were relevant (one already retrieved by Cochrane).

SumSearch—96 articles, one protocol (already retrieved by PubMed and Cochrane).

Search results—three articles found, two relevant (already retrieved by PubMed and Cochrane).

Search outcome

See table 2.

Commentary

Previous studies of administering parenteral fluid and/or alkali therapy to neonates with metabolic acidosis have included infants with clinically suspected poor perfusion (e.g. low blood pressure, poor cutaneous perfusion). Other studies of the effect of early volume expansion on mortality and morbidity have included unselected preterm infants not known to have metabolic acidosis.

We found only two studies addressing the benefit of administering intravenous bolus of albumin or normal saline to normovolaemic neonates with metabolic acidosis. They do not however provide a clear answer to the main question of this article in view of few methodological weaknesses. The first study was not blinded. The second study was not randomised and no placebo group was available. Although both studies reported an improvement in the pH and base deficit with volume expansion (although less marked than with bicarbonate), neither of these reports included the following outcomes: survival, morbidity, length of hospital stay, or neurodevelopment disability. The effect of the resulting correction of the metabolic acidosis on those clinically important outcomes therefore remains unknown.

Table 2 Treatment of metabolic acidosis in normovolaemic newborns

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Dixon *et al* (1999)	Randomised control trial using 10 ml/kg 4.5% albumin (20 babies) versus sodium bicarbonate (16 neonates) with metabolic acidosis without hypotension	Randomised control trial (level 1b)	Improvement in pH	Change in median pH following bicarbonate (0.10 units) was over twice that in the albumin group (0.04 units)*	In normotensive neonates, bicarbonate was more effective than albumin to correct the metabolic acidosis
Belgaumkar *et al* (1998)	10 ml/kg 4.5% albumin infusion in 26 ventilated normotensive neonates with metabolic acidosis	Retrospective cohort (level 4)	Improvement in pH and base deficit	Improvement in pH and base deficit up to 6 hours later ($p<0.05$), no change in blood pressure*	

*Results did not allow risk reduction and NNT to be calculated.

In the absence of outcome based data, there is currently no evidence to support the routine administration of intravenous bolus of albumin or normal saline to normovolaemic neonates with metabolic acidosis. In addition, as administration of volume expansion was found to be associated with increased mortality in preterm neonates, it is recommended that, in the absence of clear hypovolaemia, caution should be exercised when prescribing volume expansion.[3] A Cochrane protocol[4] reviewing base administration or fluid bolus for preventing morbidity and mortality in preterm infants with metabolic acidosis is currently underway and may provide the appropriate answers.

CLINICAL BOTTOM LINE

- The effect of administration of an intravenous bolus of albumin or normal saline to normovolaemic neonates with metabolic acidosis on mortality, morbidity, and neurodevelopmental outcome in this group of infants is not known.
- There is no evidence to support the benefit of this therapy for such infants.

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How safe is ibuprofen in febrile asthmatic children?

Report by
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A 4 year old child presents to the paediatric accident and emergency department with a history of fever for 12 hours and clinical signs of an upper respiratory tract infection. The temperature on assessment is 39.5℃. There is a past medical history of asthma. The attending emergency doctor prescribes ibuprofen. The mother is not willing to give ibuprofen to her child, as she was told in the past that it is contraindicated in children with asthma.

Structured clinical question

In febrile children with a past medical history of asthma [patient], is ibuprofen in antipyretic doses [intervention], compared to paracetamol [comparison], more likely to cause an acute exacerbation of asthma [outcome]?

Search strategy and outcome

Cochrane Databases of Systematic Reviews—none relevant.

Pubmed: ''Paracetamol'' OR ''Ibuprofen'' AND ''Asthma''. Limits: All child: 0–18 years, English Language; 30 hits, three relevant.

Journals@Ovid in Athens (ovid) database: ''paracetamol'' OR ''acetaminophen'' AND ''Ibuprofen'' AND ''Asthma''; 218 Hits; three relevant (one, same study as above).

See table 3.

Commentary

All three references[1–3] highlighted by Pubmed using the above search strategy were published by Lesko *et al*. The data used in all papers were originally derived from the Boston University Fever Study.[4] Therefore, the data described in 2002[2] and 1999[3] are overlapping.

The original study[4] was double blind, randomised, and controlled; patients received either paracetamol in a dose of 12 mg/kg or ibuprofen in a dose of 5 or 10 mg/kg.

To establish the asthma morbidity after the short term use of ibuprofen in children,[2] the data were restricted to include only children being treated for asthma, defined as those who had received a β-agonist, theophylline, or an inhaled steroid on the day before enrolment in the clinical trial. Morbidity from asthma was defined as a report of hospitalisation or outpatient visit for asthma in the month after enrolment.

The data suggested that there was a significantly lower rate of exacerbations of asthma in children receiving ibuprofen compared to children receiving paracetamol. The authors argue that this could be due to the anti-inflammatory action of ibuprofen.

The study by McIntyre and Hull[5] was conducted on an inpatient population, which included children with asthma or wheezing. The results showed that no child receiving ibuprofen (including 32 with asthma or a past medical history of asthma) developed symptoms of asthma or wheezing.

In both studies, patients were excluded if there was a known hypersensitivity to paracetamol, ibuprofen, aspirin, or any NSAIDs. Children were also excluded if they had nasal polyps, angioedema, or bronchospastic reactivity to aspirin or other NSAIDs. This small group of children remains potentially vulnerable to ibuprofen or other NSAIDs.

Table 3 Ibuprofen in febrile asthmatic children

Citation	Study group	Study type	Outcome	Key results	Comments
Lesko *et al* (2002)[2]	Total 1879 febrile children 6 mth–12 years receiving asthma medication **Group1**: 632 children receiving paracetamol 12 mg/kg/dose **Group 2**: 636 children receiving ibuprofen 5 mg/kg/dose **Group 3**: 611 children receiving ibuprofen 10 mg/kg/dose	Randomised controlled trial	Outpatient visits for asthma or hospitalisation for asthma during 4 weeks post-medication	69 (3.4%) documented outpatient visits: 32 in group 1 and 37 in groups 2 and 3	Ibuprofen was found to be less likely to exacerbate asthma when compared to paracetamol. Children with known hypersensitivity to paracetamol or NSAIDs were excluded
McIntyre and Hull (1996)[5]	Febrile inpatient children (2 mth–12 years) **Group 1**: 76 received ibuprofen (11 had wheeze or asthma, 21 had a history of asthma or wheezing) **Group 2**: 74 received paracetamol (4 with asthma or wheezing and 12 with a history of asthma or wheezing)	Randomised controlled trial	Change in axillary temperature, palatability, changes in clinical condition, number and nature of adverse effects	10/76 (13%) patients in the ibuprofen group had 16 adverse events, 14/74 (19%) patients in the paracetamol group had 18 events. This was statistically not significant. No patients had an asthma attack, but two became wheezy, both in the paracetamol group	The majority of all adverse events was considered to be either mild or not in relation to the treatment. Children with known hypersensitivity to paracetamol or NSAIDs were excluded

CLINICAL BOTTOM LINE

- Ibuprofen used as an antipyretic in febrile children with a past medical history of asthma is as least as safe as paracetamol and not likely to exacerbate asthma.
- Ibuprofen should not be used in children with known hypersensitivity to NSAIDs. The possibility of adverse reactions remains in children who have not received NSAIDs at any time in the past.

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