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. 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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 search- 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. To pull the information together, a commentary is provided. But to make it all much more accessible, a box provides the clinical bottom lines.

The electronic edition of this journal contains extra information to each of the published Archimedes topics. The papers summarised in tables are linked, by an interactive table, to more detailed appraisals of the studies. Updates to previously published topics will be linked to the original article when they are available.

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 compression better in resuscitating infants who have sustained a cardiac arrest?
- Is buccal midazolam an effective alternative to rectal midazolam in the treatment of status epilepticus?

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:

- Do pizotifen or propranolol reduce the frequency of migraine headache?
- Are anticonvulsants a satisfactory alternative to opiate analgesia in patients experiencing pain with Guillain-Barré syndrome?
- Is transcatheter device occlusion as good as open heart surgery for closure of atrial septal defects?

## Putting evidence into practice: part 1

Journal clubs are probably the easiest place to get evidence based medicine (EBM) started. Most attendees will be familiar with this being a place for examining papers, and it might even have a regular slot on the timetable. We’ve found that converting a traditional journal club to an evidence-based one improved attendance and interest in the event. It seems to have a lasting effect too, with ex-club members recalling the principles of EBM and the key points of critical appraisal two years after leaving the hospital (L Etheridge and H Jepps, personal communication).

An evidence based journal club is split into three uneven sections (when it’s up and running). A question is devised one week, its search results looked at the next, and the week after sees an analysis of the best paper(s). In each session, the first five minutes are used to review the results of a search, and a paper selected. The next 40–45 minutes are used to discuss a paper, and the last 5–10 minutes are used to identify and clarify a clinical question to roll onwards. In the first few weeks, teaching papers and “planted” questions can be used to get the principles in place. It also helps if the group leader can make sure that the initial questions being asked are likely to have an answer—it can be highly dispiriting to have a three week run of “no evidence for this question”. The problems you are likely to face when doing this include:

- Lack of answers to the questions asked.
- Research nihilism—no paper is perfect so no answer can be given.
- Access to papers upsetting your timetable.
- Staff changes and revisiting the basics.

The best defences to these problems are encapsulated by Baden-Powell’s motto: “Be prepared”. Have to hand the idea that only about 1/9 questions will have a decent answer; and have a few questions up your sleeve to tickle people with. Push the idea of “how good is the study” rather than “how poor is the study”. Keep a store of papers you’d use for teaching to fill in awkward gaps, and to broaden your understanding of other sorts of studies. (You’ll probably find you get lots and lots of therapeutic questions and not very many diagnostic, prognostic, or aetiologic ones.) And to get around the problem of staff changing, try to empower the group to teach itself as it goes along.

## References


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**REFERENCES**

Once again you find yourself in a busy general paediatric clinic faced with a 14 year old girl suffering from recurrent headaches for the past nine months. The history would suggest frequent attacks of a migrainous nature without aura. There is a positive family history in both parents and a sibling, but no obvious precipitating factors. The attacks are now occurring weekly and interfering with normal activities, especially school attendance. She is due to start GCSE coursework soon and both her and her parents are very keen to try a preventative medication. Her neurological examination is normal. They would like her on pizotifen or propranolol as these have helped other family members in the past. She is not asthmatic and otherwise healthy.

Structured clinical question

In an adolescent with frequent migraineous headache [patient] does the prescription of pizotifen or propranolol [intervention] reduce the frequency and/or the severity of migraine attacks [outcome]?

Search strategy and outcome

The data were derived from the results of a search carried out in 2003 by an information specialist at Clinical Evidence.

Secondary sources: The Cochrane Library, Issue 4, 2003—one relevant review found.3

Primary sources: Medline 1966 to date, Embase 1980 to date. The search terms used were: migraine AND child OR infant OR pediatric OR paediatric OR schoolchild OR teen OR teenager OR adolescent. This strategy yielded 36 systematic reviews and a further 51 randomised controlled trials. The majority were excluded as they were either irrelevant or of poor quality, leaving just five articles (see tables 1 and 2).

Commentary

Studies in the developed world suggest that migraine is the commonest diagnosis among children presenting to a medical practitioner with headache. There are well defined diagnostic criteria laid down by the International Headache Society.2 Girls and boys are affected equally before puberty, but thereafter girls are more likely to suffer migraine.2–4 Propranolol and pizotifen are widely prescribed by paediatricians as prophylactic agents.

No systematic reviews were available on the use of β blockers, though three RCTs with conflicting results were identified which compared propranolol with placebo. Ludvigsson5 showed in 32 children aged 7–16 years that propranolol (60–120 mg in three divided doses) produced a significant increase in the perception of benefit compared with placebo. Forsythe and colleagues6 showed that propranolol (40–120 mg daily) actually increased headache duration compared with placebo in 53 children aged 9–15 years. Olness and colleagues7 found no significant difference in the number of migraine attacks between propranolol (3 mg/kg per day) and placebo in 33 children aged 6–12 years. No significant harmful side effects were reported in any of these patient groups. All three studies had methodological flaws, and all, because of their small size, probably lacked the power to exclude clinically important differences and to yield important information about harms. The interpretation of post-crossover results in these three RCTs is unreliable.

Table 1. The use of propranolol as migraine prophylaxis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludvigsson (1974), Sweden</td>
<td>32 children with IHS-congruent migraine (aged 7–16 years)</td>
<td>Double-blind, crossover RCT (level 2c)</td>
<td>Increased perception of benefit of propranolol v placebo</td>
<td>Pre-crossover results: 13/13 (100%) improved with propranolol v 4/15 (27%) with placebo; p&lt;0.001; NNT = 1.4</td>
<td>Reliability may be limited because very small trial with 13% of children lost to follow-up</td>
</tr>
<tr>
<td>Forsythe et al (1984), UK</td>
<td>53 children with IHS-congruent migraine (aged 9–15 years)</td>
<td>Double-blind, crossover RCT (level 2c)</td>
<td>Propranolol significantly increased headache duration compared with placebo</td>
<td>Pre-crossover results: mean duration of headache: 436 minutes with propranolol v 287 minutes with placebo, p&lt;0.01</td>
<td>Reliability may be limited because only 74% of children completed the study</td>
</tr>
<tr>
<td>Olness et al (1987), USA</td>
<td>33 children with IHS-congruent migraine (aged 6–12 years)</td>
<td>Double-blind, crossover RCT (level 2c)</td>
<td>No significant difference in the number of episodes of migraine between propranolol and placebo at 3/12</td>
<td>Pre-crossover results</td>
<td>Confounding effect: In five participants in whom migraine was thought to be provoked by food, diet was restricted to avoid these foods. Reliability also limited by 15% drop-out rate</td>
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</tbody>
</table>
because the short washout period may introduce a confounding effect.

Very little data were found on the use of pizotifen in this setting. No systematic reviews were identified. One RCT by Gillies and colleagues\(^8\) predated the IHS diagnostic criteria and not all participants in this study would fulfil the current IHS definition for migraine, and participants would not all fulfil the current IHS definition. No systematic reviews were identified. One RCT by Salmon\(^9\) was only published in abstract form and indicated that this study was from a mixed patient group, only some of whom had ‘classical’ migraine. Furthermore, very limited numerical results are included in this abstract and so the conclusions of this study are unreliable on strength of the information provided.

### CLINICAL BOTTOM LINE

- There have only been three studies on the use of propranolol as prophylaxis in migraine, and each differs in its conclusion.\(^1\) one suggested a benefit,\(^4\) a second suggested no benefit,\(^6\) and a third concluded that it may actually worsen symptoms.\(^5\)
- There is no reliable published data to support the use of pizotifen in migraine prophylaxis.\(^2\)

### Table 2  The use of pizotifen as migraine prophylaxis

<table>
<thead>
<tr>
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<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillies et al (1986), UK</td>
<td>47 children (aged 7–14 years) Two patient groups: A (16 patients, pizotifen 0.5 mg 3/12 then placebo 3/12); B (23 patients, placebo 3/12 then pizotifen 0.25 mg 3/12) Dosing in each 3/12 block split into 6/52 b.d. then 6/52 t.d.s.</td>
<td>Double-blind, crossover RCT (level 2c)</td>
<td>No benefit of pizotifen over placebo in reducing number of attacks, total duration of attacks, duration of longest attack or mean duration of attack</td>
<td>Group A: Pizotifen vs. placebo: b.d. dosing: Number of attacks 3.0 vs. 2.5, NS; total duration of attacks 11.25 h vs. 7.8 h, NS; longest attack 6 h vs. 3.4 h, NS; mean duration of attacks 3.6 h vs. 2.0 h, NS. t.d.s. dosing: Number of attacks 1.5 vs. 2, NS; total duration of attacks 6 h vs. 7.0 h, NS; longest attack 8.8 h vs. 3.8 h, NS; mean duration of attacks 3.7 h vs 3.0 h, NS. Group B: Placebo vs. pizotifen b.d. dosing: Number of attacks 3 vs. 2, NS; total duration of attacks 9 h vs. 7.5 h, NS; longest attack 4 h vs. 3.5 h, NS; mean duration 2.4 h vs. 2.5 h, NS. t.d.s. dosing: Number of attacks 3 vs. 2, NS; total duration of attacks 8 h vs. 10 h, NS; longest attack 4 h vs. 4.5 h, NS; mean duration of attacks 3 h vs. 3.5 h, NS.</td>
<td>Study predated the IHS diagnostic criteria for migraine, and participants would not all fulfil the current IHS definition. Reliability limited as 17% of children did not complete the study.</td>
</tr>
<tr>
<td>Salmon (1985), UK</td>
<td>40 children (aged 6–15)</td>
<td>Double-blind, placebo controlled, parallel group (level 2c)</td>
<td>Not reliable</td>
<td>No numerical results data published</td>
<td>Study published in abstract form only, so methodology not open to scrutiny. Mixed patient group who would not all fulfil the IHS diagnostic criteria for migraine.</td>
</tr>
</tbody>
</table>

### Acknowledgements

We thank Clinical Evidence for the use of data from a search carried out by them in 2003.

### REFERENCES

Are anticonvulsants a satisfactory alternative to opiate analgesia in patients experiencing pain with Guillain-Barré syndrome?

Report by

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doi: 10.1136/adc.2004.054510

A 9 year old girl is admitted to the paediatric intensive care unit (PICU) with a diagnosis of Guillain-Barré syndrome (GBS). She has global motor weakness with an MRC power grade 3 and does not require mechanical ventilation. She has dysautonomia and remains on the PICU for respiratory and invasive arterial monitoring. During her admission she develops severe leg and back pain. Regular paracetamol and non-steroidal anti-inflammatories are inadvisable and so anticonvulsants are tried and tested opiate analgesia compared to gabapentin and carbamazepine, although neither is without side effects. In the absence of solid evidence currently, do anticonvulsants provide better analgesia than opiates and with fewer side effects? Your educational supervisor asks you whether anticonvulsants would be an effective analgesic, or whether the tried and tested opiates would be the best option.

Structured clinical question

In patients experiencing pain complicating Guillain-Barré syndrome, do anticonvulsants provide better analgesia than opiates and with fewer side effects?

Search strategy and outcome

Cochrane library

Guillain Barre (MeSH–explode) and pain (explode).

Thirteen hits: one relevant; 12 papers excluded because they did not address the problems of analgesia in GBS.

Are anticonvulsants a satisfactory alternative to opiate analgesia in patients experiencing pain with Guillain-Barré syndrome?

Medline database

Guillain Barre (explode all fields) and pain (explode all fields).

Twenty one hits: two relevant; 19 papers excluded (see above).

See table 3.

Commentary

The apparent success of carbamazepine, an anticonvulsant with an unknown mode of action, in the treatment of pain associated with GBS was documented as long ago as 1970. Since then, anticonvulsants have been shown to be effective in neuropathic pain of differing origin. There have been only two trials conducted in a cohort of patients with GBS that have compared the use of anticonvulsants to placebo, with opiate rescue analgesia. The trials, using either gabapentin or carbamazepine, despite small numbers, have shown both a significant reduction in opiate requirements and in the subjective perception of pain, as assessed by pain scales. The advantages to reducing the opiate requirements are obvious. In both trials the sedation scores were significantly reduced in the groups receiving anticonvulsants at that time. Improved sedation scores can lead to improved respiratory function and less time weaning from mechanical ventilation. Side effects from the anticonvulsants were not apparent.

Can we draw the conclusions above given that the data reviewed were obtained from adult patients? We believe that the data are applicable in this case. Guillain-Barré syndrome is a disease that commonly affects adults and older children but can affect children as young as infants. Pain pathways in older children are similar to those of adults and there is growing evidence that pain pathways are fully functional in the newborn. In this age of evidence based medicine there are more adult data available than paediatric, possibly secondary to difficulties of ethics, recruitment, and consent. To ignore all adult data and reproduce randomised trials in children would be time consuming, expensive, and unethical, particularly in cases such as the one cited above where the underlying pathophysiology is very similar.

<table>
<thead>
<tr>
<th>Citation</th>
<th>Patient group</th>
<th>Study type</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Study weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandey et al (2002), India</td>
<td>18 adults with GBS, pain &gt; 3 on scale 1–10; All mechanically ventilated</td>
<td>Double blinded randomised controlled cross over trial. Group 1 given gabapentin for 7 days then after 2 days washout, placebo for 7 days. Group 2 given placebo for 7 days, 2 days washout, then gabapentin</td>
<td>1. Improvement of pain scores 2. Use of rescue analgesia (2 μg/kg fentanyl) 3. Ramsay sedation score</td>
<td>1. Pain scores during PTP fell from 7.22 ± 0.83, day 0, to 2.06 ± 0.63, day 7 (p &lt; 0.001). Pain scores during PTP fell from 7.83 ± 0.78, day 0, to 5.67 ± 0.91, day 7, (nsd)*. 2. Rescue analgesia in PTP 211.1 ± 21.38 μg, day 1, fell to 65.55 ± 16.17 μg, day 7, (p &lt; 0.001). In PTP 319.44 ± 45.08 μg fell to 316.67 ± 24.25 μg (nsd).</td>
<td>Small numbers</td>
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<tr>
<td>Tripathi and Kauwashik (2000), India</td>
<td>12 adults with pain complicating GBS; All mechanically ventilated</td>
<td>Prospective, double blinded, randomly controlled cross over trial. Group 1 given placebo for 3 days, 1 day washout, then 3 days carbamazepine. Group 2 carbamazepin then placebo</td>
<td>1. Pain scores on an ordinal scale 1 to 5 2. Use of rescue analgesia (pethidine requirements) 3. Sedation score</td>
<td>1. Group 1 pain scores 4.2 ± 0.6 (control) fell to 3.5 ± 0.6, day 3, (nsd), then fell to 1.5 ± 0.6, day 7, (p &lt; 0.001). Group 2 pain scores 4.7 ± 0.5 (control) fell to 1.2 ± 0.5, day 3, (p &lt; 0.001), then rose to 3.0 ± 0.0, day 7 (nsd). 2. Rescue analgesia: Group 1 4.1 ± 0.9 mg/kg/day fell to 4.5 ± 0.4, day 3, (nsd), then fell to 0.5 ± 0.6, day 7 (p &lt; 0.05). Group 2 3.9 ± 1.0 mg/kg/day fell to 0.2 ± 0.5, day 3, (p &lt; 0.5), then rose to 3.6 ± 0.6, day 7 (nsd).</td>
<td>Small numbers</td>
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</table>

*nsd, no significant difference.
Our conclusions from studying the adult data led us to apply the findings to our paediatric practice. We do endorse the need for seeking out critically appraised “paediatric literature” where available, but to ignore all adult data is to do the child a disservice. We suggest that in circumstances similar to ours—where the pathophysiology of the disease is understood and similar to the mature state—adult data should be considered.

**CLINICAL BOTTOM LINE**
- Guillain-Barré syndrome can be associated with pain in up to 55–80% of patients.¹
- This pain tends to be of two different types: musculoskeletal and neuropathic.
- Anticonvulsants are at least as effective as opiates in treating the neuropathic pain in GBS. They have the additional advantages of reducing the opiate requirements and consequently lessening sedation scores and opiate related side effects.

**REFERENCES**

**Is transcatheter device occlusion as good as open heart surgery for closure of atrial septal defects?**

**Report by**

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doi: 10.1136/adc.2004.054486

A 6 year old boy is found to have a fixed split second heart sound and a systolic murmur heard best at the left upper sternal border on routine physical examination. The presence of a secundum atrial septal defect is confirmed by echocardiography. The attending cardiologist recommends closure via transcatheter device placement. The studious paediatric resident remembers reading in the most recent edition of the Nelson textbook of pediatrics that open heart surgery is also an acceptable option. Knowing that the consultants in her department think that EBM stands only for expressed breast milk, the resident decides to search the recent medical literature.

**Structured clinical question**
In children with atrial septal defects [patient] is transcatheter device closure [intervention] as good as surgery [comparison] at closing the defect, with fewer side effects [outcomes]?

**Search strategy and outcome**
Search engine—PubMed: “heart septal defects, atrial” and “heart catheterization” and “surgery” (MeSH-terms) limit to clinical trial, all child: 0–18 years.

Search results—11 studies found, one relevant. See table 4.

**Commentary**
While open heart surgery is the traditional means of treating atrial septal defects, transcatheter device occlusion is quickly becoming the treatment of choice in major cardiovascular centres. With this new technique, patients do not require thoracotomies or cardiopulmonary bypass, and can often be discharged from hospital on the same day as the procedure. Unfortunately, not all types of defects can be closed in this fashion, and sometimes the suitability for device closure cannot be determined until after a cardiac catheterisation has begun.

There are no randomised, controlled trials of catheter device versus surgical closure of atrial septal defects in adults or children. One non-randomised study including both adults and children compared the two methods of treatment; unfortunately, there was no subset analysis of the paediatric group.

Du et al show that closure is very successful in both patients treated with the Amplatz septal occluder (ASO) (96%) and those undergoing open heart surgery (100%) with p = 0.002. More importantly, Du et al show a decrease in major complications (p = 0.03, NNH = 28) and length of hospital stay (p < 0.001) in patients treated with ASO. Regrettably, the eligibility criteria was different between the two groups. For example, patients in the ASO group needed to have smaller, single defects and those in the surgery group could have larger, multiple defects. The right atrial and right ventricular sizes were not different between the two groups, however, indicating similar haemodynamic implications. Group allocation was decided by the patient in consultation with his cardiologist. No attempt was made to adjust for the confounders.

The evidence to date does not adequately address our clinical question. There are no trials specifically performed in children, and none with children analysed as a subset. Future clinical trials should be randomised, if possible.

<table>
<thead>
<tr>
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<th>Study type (level of evidence)</th>
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<tbody>
<tr>
<td>Du et al (2002)</td>
<td>596 patients, age 0.6–82 years, 442 in device group (ASO), mean age 18.1 ± 19.3 and 154 in surgical group (SRG), mean age 5.9 ± 6.2. Pts weighing &lt;8 kg excluded</td>
<td>Multicentre, non-randomised concurrent trial (level 2b)</td>
<td>Procedure attempt success</td>
<td>SRG = ASO for procedure attempt success: p = 0.002, NNH = 14</td>
<td>No subset analysis on paediatric patients. Intent-to-treat analysis not performed</td>
</tr>
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</table>

**Table 4 Transcatheter device versus surgical closure for secundum atrial septal defect**
CLINICAL BOTTOM LINE
- Amplatzer septal occlusion and open heart surgery both have excellent success rates in the closure of atrial septal defects.
- Patients undergoing transcatheter ASD occlusion have shorter hospital stays with fewer major complications compared to those having surgical closure.

REFERENCES

IMAGES IN PAEDIATRICS

The Good Samaritan

Sometimes Victorian sentimentality masks fundamental truths. William Small’s nineteenth century portrait of what we would today describe as an ambulatory/community paediatrician could be seen within such a sentimental light: but this is a mistake.

Painted in an era where charges for medical consultations were routine, any doctor freely ministering to the poor and needy was welcome to those who otherwise could not afford their services.

We can comment on how the child who is unwell is held up instead of being examined lying down, but we should first consider how well our own practices will stand up when examined at a similar period in the future. Or we can look at the meagre dwellings and how all the children are unshod. We can at least be thankful that some things have improved, though there is still a very long way to go before poverty is eliminated.

This picture, *The Good Samaritan*, is inspired by the Biblical parable. It does not fully show the face of the doctor and it is not based on any one individual. We are left to construct the doctor’s face for ourselves and in it we see those paediatricians who continue to inspire us.

It stands for a selfless ideal of a doctor who did not pass by a child in need.

We do not know why the doctor stopped in the midst of a busy working day, only that he has done so. The field is his consultation room and he kneels to better examine the child.

The painting reminds us that in medicine, just like life, the unexpected can happen at any time. How we respond when we see that child in need is the acid test of our professional calling and the true legacy of our inspirational predecessors.

We would like to thank the Leicester City Museums Service for permission to reproduce this portrait, which is at the New Walk Museum and Art Gallery, Leicester.

In memory of Dr Peter Daish, MD, MSc, FRCP, FRCPCH, consultant paediatrician, colleague, and friend.

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