ARCHIMEDES

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

Arch Dis Child 2003;**88**:638–642

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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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

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 available soon from the same site, with links to the original article.

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.

- Are routine chest *x* ray and ECG examinations helpful in the evaluation of asymptomatic heart murmurs?
- Does intravenous mannitol improve outcome in cerebral malaria?
- Do antipyretics prevent febrile convulsions?

Bob Phillips, Evidence-based On Call, Centre for Evidence-based Medicine, University Dept of Psychiatry, Warneford Hospital, Headington OX3 7JX, UK; bob.phillips@doctors.org.uk

REFERENCES

1 **Moyer VA**, Ellior EJ. Preface. In: Moyer VA, Elliott EJ, Davis RL, *et al*, eds. *Evidence based pediatrics and child health*, Issue 1. London: BMJ Books, 2000.
2 **Richardson WS**, Wilson MC, Nishikawa J, *et al*. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;**123**:A12–13.
3 **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.
4 **http://cebm**. jr2.ox.ac.uk/docs/levels.htm (accessed July 2002).
5 **Sackett DL**, Starus S, Richardson WS, *et al*. *Evidence-based medicine. How to practice and teach EBM*. San Diego: Harcourt-Brace, 2000.
6 **Moyer VA**, Elliott EJ, Davis RL, *et al*, eds. *Evidence based pediatrics and child health*, Issue 1. London: BMJ Books, 2000.

The duck-yak problem

It seems to be every other day that a new wonder test arrives. Yesterday it was CRP, tomorrow serum PCT may loom. How do these tests, which in early studies have such astounding sensitivity and specificity, fall by the wayside so quickly?

It doesn't have to be fraud. It may be a reflection of the duck-yak problem.* You see, when tests are first tried out, it's often in a group of patients with an advanced version of the condition (say, meningococcal septic shock) and compared with levels in a "healthy" population (for example, preoperative blood tests). The test is then very effective at separating those with septic shock (the yaks) from the healthy ones (the ducks). If a test can't tell the difference between these two groups, it's truly useless.

Clinically though, it's the next phase study you actually want. These look to see if the new wonder test actually works on the floor of the A&E department. Can it distinguish between children with a few petechiae and a cold, and those who have the early stages of meningococcal septicaemia? Here, the test is asked not to separate the yaks from the ducks but a yak from a moose—and I'm assured by Canadian colleagues this is pretty tough stuff. At this stage, the tests don't normally perform as well, and another false dawn is over.

So the moral of the duck-yak problem is this: don't ask first about the sensitivity of a new test, ask whether it was tested in an appropriate population.

* **Thanks to Killgore Trout**

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

Are routine chest *x* ray and ECG examinations helpful in the evaluation of asymptomatic heart murmurs?

Report by

Susan Gardiner, *Bradford Royal Infirmary, UK*

A 6 month old infant is referred by the GP to the general paediatric clinic with an asymptomatic heart murmur. A careful history does not reveal any symptoms of heart disease. On examination there is a soft systolic heart murmur,

Table 1 Evaluation of asymptomatic heart murmurs

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Smythe *et al* (1990)	161 children aged 1 month to 17 years with asymptomatic heart murmur referred to paediatric cardiologist	Prospective cohort (level 2b) Reference standard was echocardiography	Correct identification of a pathologic heart murmur after clinical evaluation & then ECG	ECG led to no change in diagnosis Clinical evaluation: Sensitivity = 96% Specificity = 95 % PPV = 88% NPV = 98% LR+ =19.2 LR– =0.04	Prevalence of heart murmur: up to 50% of paediatric population Paediatric cardiologist evaluating patients & ECG Independent reference standard ECHO applied to all but *not* blinded
Birkebaek *et al* (1995)	100 children aged 1 month to 15 years with asymptomatic heart murmur referred to general paediatrician	Prospective cohort (level 2b) Reference standard was echocardiography	Correct diagnosis of heart murmur after clinical evaluation then ECG & CXR	3 abnormal ECGs all evaluated to have heart disease after clinical evaluation CXR: Sensitivity = 43% Specificity = 82% PPV=42% NPV= 83% LR+ = 2.36 LR– = 0.70	Independent reference standard ECHO applied blindly to all patients No prevalence for heart murmurs given
Birkebaek *et al* (1999)	100 children aged 1 month to 15 years with asymptomatic heart murmur referred to general paediatrician	Prospective cohort (level 2b)	Accuracy of chest *x* ray evaluation by paediatric radiologists	Mean intra-observer k value: All films = 0.452 Normal films = 0.320 Abnormal films = 0.595 Mean inter-observer k value: All films = 0.282 Normal films = 0.106 Abnormal films = 0.531	Same cohort of patients as in above paper Interpretation of chest *x* ray by a paediatric radiologist is only poorly to moderately reproducible
Temmerman *et al* (1991)	284 children referred to paediatric cardiologist for cardiology evaluation aged 0.5–17 years (nearly all heart murmurs)	Prospective cohort (level 3b) Reference standard was echocardiography	Correct diagnosis of a heart murmur after clinical evaluation & then CXR	CXR led to diagnosis of heart disease in 2.8% of patients diagnosed with normal heart after primary evaluation In 2.8% of patients with a diagnosis of heart disease after 1st evaluation CXR led to a change in diagnosis to no heart disease	No prevalence given for heart murmurs Not specified asymptomatic heart murmurs CXR not performed in all referred patients Reference standard ECHO not applied to all patients
Swenson *et al* (1997)	106 children aged 1 month to 14 years with heart murmur or chest pain, referred to paediatric cardiologist	Prospective cohort (level 4) Reference standard was echocardiography	Correct diagnosis of heart murmur after clinical evaluation then ECG & CXR	4 patients evaluated normal heart, diagnosed heart disease on basis of ECG & CXR 3 patients ECG & CXR misled diagnosis	ECHO only applied to 45/106 patients Patients included with chest pain ?skewed results as higher proportion of abnormal ECGs than previous studies
Rajakumar *et al* (1999)	128 children aged 1 month to 18 years referred to paediatric cardiologist with a heart murmur	Prospective cohort study (level 4) Reference standard was echocardiography	Correct diagnosis of heart murmur by general paediatrician compared to paediatric cardiologist after clinical evaluation then ECG & CXR	General paediatricians clinical evaluation alone/after ECG & CXR Sensitivity = 79%/82% Specificity = 55%/54% PPV = 39%/39% NPV = 88%/89% LR+ = 1.76/1.78 LR– = 0.38/ 0.33 Paediatric cardiologist clinical evaluation alone/after ECG & CXR Sensitivity = 85%/88% Specificity = 77%/70% PPV = 57%/51% NPV = 93%/94% LR+ = 3.7/2.9 LR– = 0.19/ 0.17 General paediatrician: ECG & CXR helpful in 2 cases & misleading in 3 cases Paediatric cardiologists: ECG & CXR misleading in 9 cases & helpful in 5 cases	Reference standard was applied blindly to all 128 patients but 28 patients were excluded from the study (as no ECHO was performed as deemed no heart disease by paed. cardiologists)

but the infant is otherwise normal. You suspect that the child has an innocent heart murmur but are not 100% sure. In this case will a chest *x* ray and ECG examination add to your clinical evaluation?

Structured clinical question

In children with an asymptomatic heart murmur [patient] does a chest *x* ray and/or ECG examination [intervention] assist in the diagnosis or exclusion of congenital heart disease [outcome]?

Search strategy and outcome

Secondary sources: none

Primary sources: Medline 1966 to October week 2, 2001: (heart murmurs OR (heart murmur$ OR cardiac murmur$).tw.) AND (electrocardiography OR ECG.mp) AND

(radiography, thoracic.mp. OR chest xray.mp, OR chest x-ray.mp OR chest radiograph.mp) AND (heart defects, congenital/ OR congenital heart disease.mp OR heart defects congenital/ra); filters children <0–18years> & English language.

Serendipity: 1 article.

Search results—132 articles found; 10 articles relevant to clinical question; four excluded due to poor quality. See table 1.

Commentary

Paediatric cardiologists have undertaken most of the research investigating the assessment of the child with a heart murmur, with and without ECG and chest *x* ray examination. However, the Birkebaek *et al* study evaluates the general paediatricians' assessment of a heart murmur and the Rajakumar *et al* study compared academic general paediatricians and paediatric cardiologists. I could find no studies comparing trainees and consultants.

In the study by Rajakumar *et al*, general paediatricians and paediatric cardiologists each evaluated the patient referred with a heart murmur (blind to the others' assessment) and classified them innocent, possibly pathologic or pathologic murmur. They then had a chest *x* ray and ECG examination and were reclassified. An echocardiogram was then performed, which gave them a definitive diagnosis. The paediatricians classified more innocent murmurs as pathologic and the cardiologists identified more innocent murmurs correctly. After ECG and chest *x* ray examination paediatricians revised five diagnoses, three incorrectly. That is, for the vast majority ECG and chest *x* ray examination did not help in the diagnosis, and in those cases where it was thought helpful it was often misleading.

The likelihood ratio of a test, calculated from the sensitivity and specificity, gives an estimate of increased probability of correctly identifying a condition (positive likelihood ratio) or excluding a diagnosis (negative likelihood ratio) when using the diagnostic tool in question. A reasonable pretest probability is assumed and then, using Fagan's likelihood ratio nomogram, the post-test probability is calculated (see Archimedes in January 2003). For example, if the pretest probability of a pathological heart murmur was 5%, an abnormal chest *x* ray examination (with a likelihood ratio of 2.36 (Birkebaek *et al*)) would make the post-test probability of cardiac pathology only about 10%. It was only possible to calculate likelihood ratios for chest *x* ray examination in one paper and the other likelihood ratios were calculated for clinical evaluation. Interestingly in the Rajakumar *et al* study the likelihood ratios after ECG and chest *x* ray examination were very similar to those after clinical evaluation—that is, little was added by doing these tests.

Birkebaek *et al* evaluated the accuracy of the paediatric radiologists in their interpretation of chest *x* rays of children with heart murmurs. This paper is relevant as most paediatricians will rely on the report from the radiologist. The six radiologists were each asked to report on all the films blind to the result of the echocardiogram, and six months later the chest *x* rays were re-evaluated by the same radiologists. The results showed only poor to moderate agreement between radiologists, and more surprisingly poor agreement when the same radiologist reviewed the films six months later.

Overall, it appears from the above research that ECG and chest *x* ray examination add little to the clinical evaluation of the child with an asymptomatic heart murmur. Concerns about a pathological cause after clinical examination should prompt a referral to a paediatric cardiologist for further assessment.

CLINICAL BOTTOM LINE

- ECG rarely adds to clinical evaluation of an asymptomatic heart murmur. It rarely leads to a change in diagnosis.
- Chest *x* ray examination is often misleading in the evaluation of an asymptomatic heart murmur and interpretation is only poorly to moderately reproducible.

REFERENCES

Smythe JF, Teixeira OH, Vlad P, *et al*. Initial evaluation of heart murmurs: are laboratory tests necessary? *Pediatrics* 1990;**86**:497–500.

Birkebaek NH, Hansen LK, Oxhoj H. Diagnostic value of chest radiography and electrocardiography in the evaluation of asymptomatic children with a cardiac murmur. *Acta Paediatr* 1995;**84**:1379–81.

Birkebaek NH, Hansen LK, Elle B, *et al*. Chest roentgenogram in the evaluation of heart defects in asymptomatic infants and children with a cardiac murmur: reproducibility and accuracy. *Pediatrics* 1999;**103**:e15.

Temmerman AM, Mooyaart EL, Taverne PP. The value of the routine chest roentgenogram in the cardiological evaluation of infants and children. A prospective study. *Eur J Pediatr* 1991;**150**:623–6.

Swenson JM, Fischer JM, Miller SA. Are chest radiographs and electrocardiograms still valuable in evaluating new pediatric patients with heart murmurs or chest pain? *Pediatrics* 1997;**99**:1–3.

Rajakumar K, Weisse M, Rosas A, *et al*. Comparative study of clinical evaluation of heart murmurs by general pediatricians and pediatric cardiologists. *Clin Pediatr (Phila)* 1999;**38**:511–18.

Does intravenous mannitol improve outcome in cerebral malaria?

Report by

Richard J Tomlinson, *Oshakati State Hospital, Namibia*

John Morrice, *Mzuzu Central Hospital, Malawi*

You are working in an African hospital during the malaria season. A 10 year old boy is admitted in coma with a fever after having had a convulsion at home.

A blood slide shows asexual forms of *Plasmodium falciparum*, his blood sugar has been checked to be normal, and he has been loaded with intravenous quinine. Antibiotics have been given until meningitis can be excluded by a normal lumber puncture. Local experience suggests intravenous mannitol is of benefit in unconscious patients with cerebral malaria; its use however, is not recommended by the World Health Organisation.[1]

Structured clinical question

In a child with cerebral malaria [patient] will intravenous mannitol [intervention] improve mortality or neurological morbidity [outcome]?

Search strategy and outcome

Medline 1966 to January 2003 using the PubMed interface (mannitol AND malaria); no limits applied.

There was a yield of just 15 articles, none being a relevant controlled trial. Further searches of related articles quoted in references found no controlled trial of mannitol use in cerebral malaria.

Commentary

Only one article was found which was relevant to the clinical question. This study[2] described the use of mannitol in 14 children with cerebral malaria (see table 2). Intracranial pressure was lowered in all cases and outcome was good or reasonable in all except the four with severe intracranial hypertension. However, there was no control group with which to compare the benefit of mannitol on case fatality or neurological outcome.

Table 2 Intravenous mannitol in cerebral malaria

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Newton *et al* (1997)	23 Kenyan children with confirmed *Plasmodium falciparum* cerebral malaria had intracranial pressure monitored. The 14 with severe and intermediate intracranial hypertension received intravenous mannitol	Uncontrolled clinical trial	Intracranial pressure Neurological outcome or mortality	Mannitol lowered the intracranial pressure in all children Of the 4 children with severe intracranial hypertension, 2 died and 2 had severe neurological sequelae. Of those with intermediate intracranial hypertension, all survived. 8 had a good outcome, 1 developed hemiparesis, and 1 learning difficulty	Primary focus of study and outcome measured was measurement of intracranial pressure in cerebral malaria

CLINICAL BOTTOM LINE

- There are no controlled data supporting the use of mannitol for cerebral malaria. Consensus statements should be followed.

Intracranial hypertension as a feature of cerebral malaria probably contributes to the poor neurological outcome and death of many children with *Plasmodium falciparum* malaria. A likely cause is an increase in cerebral blood volume due to sequestered parasitised erythrocytes. Mannitol is a relatively cheap osmotic agent which appears to lower intracranial pressure. This may potentially improve the survival and neurological outcome of many children with cerebral malaria. Anecdotal evidence suggests that the conscious level of children with cerebral malaria improves with intravenous mannitol; however, when it should be used is unknown. The benefit may only be temporary; however, in resource limited settings where intensive nursing care may not be optimal, shortening the duration of a coma may have benefits for neurological outcome.

The WHO emphasise that none of the ancillary treatments for cerebral malaria have sufficient supporting evidence to be used. No controlled study for the use of mannitol in paediatric or adult cerebral malaria could be identified and its use can not be recommended. Further studies are necessary to determine its value and potential side effects.

REFERENCES

1 **Warrell DA**, Molyneux ME, Beales PF. World Health Organisation, Division of Control of Tropical Diseases. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990;**84**(suppl 2):1–65.
2 **Newton CR**, Crawley J, Sowumni A, *et al*. Intracranial hypertension in Africans with cerebral malaria. *Arch Dis Child* 1997;**76**:219–26.

Do antipyretics prevent febrile convulsions?

Report by
A Sahib El-Radhi, W Barry, *Queen Mary's Hospital, Sidcup, Kent, UK*

A 1 year old child is admitted following their first febrile seizure (FS). We wish to prevent recurrences during further febrile episodes. The nursing staff ask you to prescribe an antipyretic. Later you come to advise the parents on methods of preventing further febrile seizures.

Structured clinical question

In children who have experienced a febrile seizure [patient] does prescribing antipyretics [intervention] reduce recurrences of febrile seizures [outcome]?

Search strategy

Secondary sources

Cochrane Library and DARE—"febrile convulsions/seizures and antipyretics", "febrile convulsions/seizures and paracetamol", "febrile convulsions/seizures and ibuprofen"; one systematic review found (paracetamol for treating fever in children); two protocols.

Prodigy Evidence Based Clinical guidance—"febrile convulsions"; nil relevant found.

Primary resources

Pubmed clinical queries (1966 to Jan 2003): "antipyretics and febrile convulsions"—80 references. Of these, three were randomised controlled trials but one was irrelevant (investigating antipyretic effects rather than subsequent seizure reduction).

Commentary

As the essential precursor of a febrile seizure is a fever, physicians and paediatric nurses have concluded that antipyretic measures should prevent febrile seizures. Antipyretics continue to be among the most commonly prescribed medications, especially for children at risk of such seizures. Parents are usually advised that the administration of antipyretics to at risk children may reduce the risk of further convulsions. When asked, the majority of medical trainees and paediatric nurses in our unit replied that the reason for giving paracetamol to children who were at risk of febrile seizure recurrence was to prevent further convulsions. However, the evidence suggests that antipyretics have no effect on preventing further febrile seizures. At this hospital, 13% of children admitted with their first FS subsequently developed repeated FS soon after admission despite the routine administration of paracetamol to control fever prior to the seizure.[1]

Children with high risk of recurrences of FS (complex features of FS, family history of FS, age less than 1 year, low grade fever at the onset of FS) develop recurrences in at least 80% while those without these risk factors rarely develop recurrences. Antipyretics are used for both groups of children, suggesting that it is these risk factors, and not antipyretics, which are the crucial determinants of the risk of recurrence.

Controlled studies of antipyretic medications, given during the original acute illness following a febrile seizure or during subsequent febrile episodes have failed to show a preventive effect in children at risk of FS (table 3). A randomised, placebo controlled trial in children at risk of FS found no evidence that paracetamol, with or without diazepam, was effective in preventing FS during subsequent febrile episodes.[2] A second

Table 3 Antipyretics in febrile seizures

Citation	Study group	Study design (level of evidence)	Outcome	Key result	Comments
Uhari *et al* (1995)	180 children after first febrile seizure randomised to 4 groups: a) placebo + placebo b) placebo + paracetamol c) diazepam + paracetamol d) diazepam + placebo	Randomised double blind placebo controlled trial (level 1b)	Number of recurrence of FS	a) 14 (25.4%) b) 9 (16.4%) c) 14 (25.5%) d) 18 (32.7%) (no statistical difference)	Duration of follow up: two years
Schnaiderman *et al* (1993)	104 children after first febrile seizure randomised to two groups: a) paracetamol 4-hourly b) paracetamol as required	Randomised controlled trial (level 1b)	Early recurrence of FS	a) Regular paracetamol = 4 (7.5%) b) PRN paracetamol = 5 (9.8%) (p = not significant)	In hospital only (no follow up)
Van Stuijvenberg *et al* (1998)	230 children after first febrile seizure randomised to: a) ibuprofen (n=111) b) placebo (n=119)	Randomised double blind placebo controlled trial (level 1b)	Number of recurrence of FS	a) 31 (35.7%) b) 36 (33%) (p = not significant)	Mean duration of follow up 1.04 y
Von Esch *et al* (2000)	Treatment group with: a) ibuprofen or paracetamol (n=109) b) no antipyretics (n=103)	Non-randomised controlled trial (level 2a)	Number of recurrence of FS	Recurrence risk per fever: a) 6.3% (treatment group) b) 12.2% (control group) ARR = 5.9%; (95% CI: –0.2% to 12%)	
Meremikwa *et al* (2002)	RCTs with paracetamol compared to placebo	Systematic review (level 1a)	Number of recurrence of FS	Conclusion: no evidence that paracetamol is effective in preventing FS	

CLINICAL BOTTOM LINE

- There is no evidence that antipyretics reduce the risk of subsequent febrile convulsions in at risk children.
- Prescription of paracetamol following febrile seizures may provide comfort and symptomatic relief, but should not be recommended to prevent further febrile convulsions.

randomised trial compared the antipyretic effectiveness of paracetamol administered at regular intervals (group 1) versus paracetamol administered at the time of fever (group 2) in children presenting with an FS. Early recurrences of FS (within the first 24 hours) were similar in both groups.[3] Ibuprofen was also evaluated in a randomised, double blind, placebo controlled trial in children at risk of FS. The recurrence rate was similar in both groups.[4] In another open trial, children at risk of FS were offered either ibuprofen or paracetamol during subsequent febrile episodes or else no medication. The recurrence risk of FS was similar in all groups.[5] These four studies concluded that the antipyretics paracetamol and ibuprofen had no preventive effect on the recurrence of FS. A recent review[6] of trials assessing the effects of paracetamol on the clearance time of fever and on FS identified 12 randomised or quasi-randomised controlled trials. It concluded that the trials failed to show any convincing evidence that paracetamol is effective in reducing fever or preventing FS.

While antipyretics may have a role in improving comfort and general wellbeing, we should surely not be advocating medication for purposes that have been shown not to work.

REFERENCES

1 **El-Radhi AS**. Lower degree of fever is associated with increased risk of subsequent convulsions. *Eur J Paediatr Neurol* 1998;**2**:91–6.

2 **Uhari M**, Rantala H, Vainionpaa L, *et al*. Effects of acetaminophen and of low intermittent doses and diazepam on prevention of recurrences of febrile seizures. *J Pediatr* 1995;**126**:991–5.

3 **Schnaiderman D**, Lahat E, Sheefer T, *et al*. Antipyretic effectiveness of acetaminophen in febrile seizures: ongoing prophylaxis versus sporadic usage. *Eur J Pediatr* 1993;**152**:747–9.

4 **Van Stuijvenberg M**, Derksen-Lubsen G, Steyerberg EW, *et al*. Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile recurrences. *Pediatrics* 1998;**102**:1–7.

5 **Van Esch A**, Steyerberg EW, Moll HA, *et al*. A study of the efficacy of antipyretic drugs in the prevention of febrile seizure recurrence. *Ambulatory Child Health* 2000;**6**:19–26.

6 **Meremikwu M**, Oyo-Ita A. Paracetamol for treating fever in children. *The Cochrane Database of Systematic Reviews* 2002;4.

The duck-yak problem. Illustration by Jack Maypole, MD