ARCHIMEDES

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

Arch Dis Child 2003;**88**:1131–1135

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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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 which have been published since the last edition include:

- Does iron have a place in the management of breath-holding spells?
- Does magnesium sulphate have a role in the management of paediatric status asthmaticus?
- Is melatonin likely to help children with neurodevelopmental disability and chronic severe sleep problems?

Hierarchical searches

Archimedes wants to answer clinical questions using a hierarchical search process. What exactly does this mean? And why is it important anyway?

The hierarchical search aims to look for the best quality evidence first, and work downwards if insufficient research is discovered. Secondary sources are looked through in the first instance. These sources have done some of the work of critical appraisal already. An excellent secondary resource is the Cochrane Library. This database contains a large number of systematic reviews of the effects of healthcare interventions, both ''Cochrane'' reviews, and in collaboration with the NHS York Centre for Reviews and Dissemination, other published systematic reviews. Other secondary sources include the *EBM Journal*, which takes good quality studies published in other journals, creates an independent abstract of the paper, and is accompanied by a critical analysis and commentary. Some guidelines are excellent sources of information, and the authors may have done the job of collating and appraising all relevant evidence for you.

Searching in secondary sources is relatively easy: the Cochrane library is all in one place,[1] *EBM Journal* lives elsewhere,[2] and a very large number of guidelines are available at the redeveloped (US) National Guidelines Clearinghouse.[3]

Where a secondary resource doesn't provide enough of an answer, *Archimedes* authors look back to the primary literature and perform a systematic, but limited, review of the studies they find. For interventions, randomised controlled trials (RCTs) are the preferred source of evidence. For medical interventions, there are empirical observations which show that non-randomised studies tend to exaggerate treatment effects.[4] If these can't be found, it may be useful to look for large cohort studies. These have many more problems than RCTs, with difficulty assessing the presence of extraneous (confounding) factors which provide an alternative explanation for the outcomes observed. However, they are more likely to estimate the true effect than most case-control studies. In turn, a case-control study has a jump on the case study (which is, after all, a posh way of saying ''anecdote'').

How do you search for these studies though? Typing ''heart attack'' into Medline may induce one. There are a few ways to assist the practicing clinician in their searching, by filtering out methodologically poor studies and presenting those with a greater chance of success. If you have the opportunity, many health information specialists (a.k.a. librarians) run courses on searching for clinical information. Alternatively you might like to look at the Clinical Queries section of PubMed[5] or the superb ''SumSearch'' engine.[6] Good luck.

References

1 http://www.cochranelibrary.com/cochrane/.
2 http://www.evidencebasedmedicine.com.
3 http://www.guidelines.gov.
4 **Schulz KF**. Randomised trials, human nature and reporting guidelines. *Lancet* 1996;**348**:596–8.
5 http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html.
6 http://sumsearch.uthscsa.edu.

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.

- Is indomethacin or ibuprofen better for medical closure of the patent ductus arteriosus?
- Should a prolonged or short course of indomethacin be used in preterm infants to treat patent ductus arteriosus?
- What is the use of the glass test?

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, 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.

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

Should a prolonged or short course of indomethacin be used in preterm infants to treat patent ductus arteriosus?

Report by
Sachin Shah, *Hospital for Sick Children and University of Toronto; sshahdoc@hotmail.com*

A 27 week gestation infant is diagnosed to have a significant patent ductus arteriosus (PDA) on echocardiography on day 2. The infant is ventilator dependent. You decide to treat with indomethacin. The resident suggests that it would be better if prolonged indomethacin therapy could be administered over 5–7 days to ensure that the PDA remains closed. What evidence did she have?

Structured clinical question

In preterm infants with patent ductus arteriosus [patient], is prolonged course indomethacin [intervention] better than shortcourse conventional therapy [comparator] in preventing recurrences and decreasing the need for surgical ligation [outcomes]?

Search strategy and outcome

Medline (1966–Dec 2002): ''indomethacin'' AND ''patent ductus arteriosus'' AND ''infant, newborn''; LIMIT to ''english language'' and ''human''—375 references. Other databases searched were Cochrane Controlled Trials Register (Issue 4, 2002), EMBASE (1980–Dec 2002), CINAHL (1982–Dec 2002), abstracts published in *Pediatric Research* (1990–2002). Five relevant trials were identified. See table 2.

Clinical bottom line

- The evidence is inconclusive as to which is the superior regimen.
- The prolonged course regime may have a role in those with borderline impairment of renal function.

Commentary

The five RCTs comparing prolonged versus short course indomethacin differ in the dosage regimes (for both prolonged and short course groups), diagnosis of PDA, and onset of treatment. Also there is a wide variation in the gestational age and birth weight.

In all but one study (Rennie *et al*), PDA was diagnosed by echocardiography. In two studies (Lee *et al*; Rhodes *et al*), PDA was detected on echocardiographic screening at predetermined intervals, while in two studies (Tammela *et al*; Hammerman *et al*), a clinically symptomatic PDA was confirmed on echocardiography.

There is significant ''in between study heterogeneity'' as far as outcomes like failure of PDA closure, need for surgical ligation, recurrence of PDA, and mortality rates are concerned.

In the majority of studies, the incidence of renal side effects was less in the prolonged indomethacin group compared to the short course group. There were no significant differences in the other co-morbidities.

In theory, short term indomethacin therapy suppresses dilator prostanoids and facilitates ductal constriction. This transient suppression may not allow sufficient time for anatomic ductal closure in many infants. This may be especially true for the extremely low birth weight infant whose PDA is more sensitive to prostaglandins and whose PDA does not constrict as tightly as the more mature infant. Also the ductus tends to retain its sensitivity for a longer duration, making it more susceptible to reopening.

This theoretical advantage has not translated into clinical practice in all the studies. The evidence is inconclusive as to which is the superior regimen. Further trials are needed to determine the optimum regimen and dose of indomethacin, especially in extremely low birth weight infants (<1000 g). A four arm trial where infants are randomised and allocated at birth, either to prolonged therapy or to short course therapy, may be the most efficient trial design. Within the prolonged and short course treatment arms, the infants would then be randomised to receive indomethacin on echocardiographic determination of PDA within the first seven days or when the PDA becomes clinically symptomatic. The outcomes assessed should be mortality and need for surgical ligation.

REFERENCES

Rhodes PG, Ferguson MG, Reddy NS. Effects of prolonged versus acute indomethacin therapy in very low birth infants with patent ductus arteriosus. *Eur J Pediatr* 1988;**147**:481–4.
Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. *J Pediatr* 1990;**117**:771–6.
Rennie JM, Cooke RWI. Prolonged low dose indomethacin for persistent ductus arteriosus of prematurity. *Arch Dis Child* 1991;**66**(1 spec no):55–8.
Tammela O, Ojala R, Iivainen T, *et al*. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. *J Pediatr* 1999;**134**:552–7.
Lee J, Rajadurai S, Wong KY, *et al*. Comparing two indomethacin dosing regimes for treating patent ductus arteriosus (PDA): a randomised controlled trial. *Pediatr Res* 2001;**49**:387A.

Table 2 Prolonged versus short course indomethacin in treatment of patent ductus arteriosus in preterm infants

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Rhodes *et al* (1988)	70 preterm infants <1500 g with echocardiographically diagnosed PDA were randomised to either prolonged course indomethacin over 1 week or to short course (2 doses of indomethacin; n=36). All infants were given 2 doses of indomethacin 0.15 mg/kg 12 hours apart. The prolonged course group (n=34) received additional 0.1 mg/kg once daily hourly × 5 days.	Prospective randomised controlled trial (level 1b)	Closure after first course	RR 1.11 (95% CI 0.77 to 1.61); RD 0.06 (95% CI −0.16 to 0.29)	No blinding of intervention. No differences in mortality rates.
			Recurrence of PDA	RR 1.51 (95% CI 0.65 to 3.52); RD 0.10 (95% CI −0.10 to 0.30)	
			Need for surgical ligation	RR 2.12 (95% CI 0.20 to 22.30); RD 0.03 (95% CI −0.06 to 0.13)	
Hammerman and Aramburo (1990)	39 infants <1500 g with echocardiographically confirmed PDA were randomised to receive standard indomethacin therapy (0.2 mg/kg/dose 8 hourly), followed by either maintenance indomethacin (0.2 mg/kg once daily × 5 days; n=20) or equivalent volume of placebo for 5 days (n=19).	Prospective randomised controlled trial (level 1b)	Closure after first course	RR 1.22 (95% CI 0.90 to 1.66); RD 0.16 (−0.07 to 0.40)	Double blind study. There was no increase in the toxic effects of indomethacin.
			Recurrence of PDA	RR 0.11 (95% CI 0.01 to 1.84); RD −0.21 (95% −0.41 to −0.01)	
			Need for surgical ligation	RR 0.14 (95% CI 0.02 to 1.00); RD −0.32 (−0.56 to 0.08); NNT 3.0 (95% CI 2 to 12)	
Rennie and Cooke (1991)	Total of 121 infants <2500 g with clinical signs of PDA were randomised to receive either prolonged course indomethacin (0.1 mg/kg once daily × 6 days; n=59) or short course (0.2 mg/kg 12 hourly × 3 doses; n=62).	Prospective randomised controlled trial (level 1b)	Closure after first course	RR 1.16 (95% CI 0.99 to 1.36); RD 0.12 (95% CI −0.01 to 0.25)	No blinding. Echocardiography was not used for assessment of PDA. Higher mortality rate in the prolonged indomethacin group, not directly related to treatment. Majority occurred after the first month.
			Recurrence of PDA	RR 0.61 (95% CI 0.32 to 1.17); RD −0.12 (95% CI −0.27 to 0.03)	
			Need for surgical ligation	RR 1.58 (95% CI 0.27 to 9.10); RD 0.02 (95% CI −0.05 to 0.09)	
Tammela *et al* (1999)	61 infants of gestational ages 24–32 wk with a PDA confirmed with echocardiography were randomised to receive short course indomethacin (3 doses of 0.2, 0.1, and 0.1 mg/kg in 24 hours; n=31) or prolonged course (0.1 mg/kg q 24 hourly × 7 days). Echocardiography was performed 3, 9, and 14 days after starting treatment.	Prospective randomised controlled trial (level 1b)	Closure after first course	RR 0.71 (95% CI 0.54 to 0.93); RD −0.27 (−0.46 to −0.08)	Only assessment was blinded. No difference in mortality rates.
			Need for surgical ligation	Increased need for surgical ligation in the prolonged group [RR 4.65 (95% CI 1.09 to 19.78); RD 0.24 (95% CI 0.05 to 0.42); NNH 4.0 (95% CI 2 to 20)]	
			Recurrences needing treatment	RR 1.03 (95% CI 0.37 to 2.85); RD 0.01 (−0.19 to 0.21)	
Lee *et al* (2001)	Infants ⩽1500 g with a symptomatic PDA greater or equal to 1.5 mm on echocardiography were randomised to conventional indomethacin (0.2 mg/kg/dose q 12 hourly × 3 doses; n=70) or prolonged low dose course indomethacin (0.1 mg/kg q 24 hourly × 6 doses; n=70).	Prospective randomised controlled trial (level 1b)	Closure after first course	Relative risk (RR) 1.02; 95% CI 0.87 to 1.27; risk difference (RD) 0.01; 95% CI −0.14 to 0.17.	No blinding of intervention. Intention to treat analysis. PDA diagnosis by echocardiography. No difference in mortality rates.
			Need for surgical ligation of PDA	RR 0.62 (95% CI 0.27 to 1.39); RD −0.07 (−0.19 to 0.05)	

Is indomethacin or ibuprofen better for medical closure of the patent ductus arteriosus?

Report by
Erik N Swartz, *Assistant Professor, Department of Pediatrics, University of Alberta, Edmonton, Canada; erikswartz@cha.ab.ca*

A preterm baby of 28 weeks gestation with respiratory distress syndrome is admitted to the neonatal intensive care unit. On day 2 of life, the characteristic murmur of a patent ductus arteriosus (PDA) is heard, with the diagnosis confirmed by Doppler echocardiography. The attending neonatologist orders a course of indomethacin in an attempt to treat the PDA. The astute paediatric resident has just taken two tablets of ibuprofen to treat his post-call headache, and wonders whether this alternative non-steroidal anti-inflammatory drug might be just as efficacious, with less side effects.

Structured clinical question

In a preterm baby of gestational age less than or equal to 34 weeks [patient] is ibuprofen [intervention] compared with indomethacin [comparison intervention] equally efficacious at treating echocardiographically proven patent ductus arteriosus and have fewer side effects [outcomes]?

Search strategy and outcome

Search engine—Cochrane library: ''ductus arteriosus, patent'' and ''indomethacin'' and ''ibuprofen'' (MeSH-Terms); PubMed: ''ductus arteriosus, patent'' and ''indomethacin'' and ''ibuprofen'' (MeSH-Terms) limit to clinical trial.

Search results—two systematic reviews: nil relevant. Two protocols for a Cochrane review: one relevant. Nine clinical studies found, four of which were relevant. See table 1.

Commentary

All four studies were randomised, controlled trials; however, the methods of randomisation were not reported. All used cards in sealed envelopes as the system of allocation concealment. Furthermore, there is no evidence that neonatologists, nurses, or pharmacists were blinded in any study. Echocardiographers were blinded in two of the studies.

Each study clearly shows the equivalence of ibuprofen and indomethacin in the treatment of patent ductus arteriosus. In addition, three studies showed a significant increase in oliguria among patients treated with intravenous indomethacin, and two studies showed a significant increase in serum creatinine. No study showed a difference in death, necrotising enterocolitis, or progression of intracranial haemorrhage between the two groups. All trials used a ''high'' dose of

Table 1 Ibuprofen versus indomethacin in the treatment of patent ductus arteriosus (PDA)

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Lago *et al* (2002)	175 preterm neonates, GA ⩽ 34 wk, postnatal age 48–72 h with echo proven PDA. Very ill babies excluded. IBU (10 mg/kg iv [time 0], 5 mg/kg iv [time 24,48 h]) v INDO (0.2 mg/kg iv q12 h×3)	RCT (level 1b) Jadad score: 2	Echo proven closure of PDA. Oliguria Post-treatment serum creatinine.	IBU = INDO for closure of PDA: ARR = 0.043 [95% CI −0.092 to 0.177] INDO more likely to produce oliguria: p = 0.017, NNH = 7 INDO resulted in higher post-treatment creatinine (mean 89 μmol/l, SD 24) than IBU (mean 81 μmol/l, SD 20): p = 0.03.	Only echocardiographers were noted to be blinded. Randomisation method not given. Allocation concealment by sealed envelope.
Van Overmeire *et al* (2000)	148 preterm neonates, GA ⩽ 32 wk, postnatal age 48–96 h with echo proven PDA. Very ill babies excluded. IBU (3 doses) *v* INDO (3 doses), same doses as above.	RCT (level 1b) Jadad score: 2	Echo proven closure of PDA Oliguria Post-treatment serum creatinine Multiple logistic regression performed to determine predictors of oliguria	IBU = INDO for closure of PDA: ARR = 0.041 [95% CI −0.109 to 0.19]. INDO more likely to produce oliguria: p = 0.03, NNH = 8 INDO resulted in higher post-treatment creatinine: p = 0.04. Independent predictors of oliguria were INDO treatment, high frequency ventilation, increased serum creatinine days 1–3, and lower ductul shunt velocity.	Only echocardiographers were noted to be blinded. Randomisation method not given. Allocation concealment by sealed opaque envelope.
Van Overmeire *et al* (1997)	40 preterm neonates, GA ⩽ 33 wk, postnatal age 48–72 h with echo proven PDA. Very ill babies excluded. IBU (3 doses) *v* INDO (3 doses), same doses as above.	RCT (level 1b) Jadad score: 2	Echo proven closure of PDA Oliguria Post-treatment serum creatinine	IBU = INDO for closure of PDA: ARR 0.05 [95% CI −0.208 to 0.308] INDO more likely to produce oliguria: p = 0.02, NNH = 3. IBU = INDO for post-treatment serum creatinine: p = 0.07	Randomisation method not given. Allocation concealment by sealed envelope. No blinding reported.
Supapannachart *et al* (2002)	18 preterm infants (mean GA 30 weeks) with PDA based on clinical and *x* ray criteria. Very ill babies excluded. IBU (10 mg/kg po od × 3 days) *v* INDO (0.2 mg/kg po/iv q12 h × 3 doses)	RCT (level 3b) Jadad score: 2	Clinical closure of PDA Oliguria Post-treatment serum creatinine	IBU = INDO for closure of PDA: ARR 0.111 [95% CI −0.229 to 0.452] No significant difference after day 1. No significant difference.	Randomisation method not given. Allocation concealment by sealed envelope. No blinding reported. INDO group was mixed between babies receiving oral and intravenous treatment; no attempt at subset analysis.

Clinical bottom line

- Intravenous ibuprofen is equivalent to intravenous indomethacin in the treatment of PDA in neonates.
- Patients receiving intravenous ibuprofen have a smaller rise in serum creatinine, and are less likely to develop oliguria (NNT = 6) than those receiving intravenous indomethacin.

0.2 mg/kg every 12 hours for three days, as opposed to the ''low'' dose of 0.1 mg/kg daily for six days.

The recent Thai study attempts to compare oral ibuprofen with indomethacin; however, analysis is very difficult as patients in the indomethacin group received the drug by different routes of administration (some oral, some intravenous). Further trials with oral ibuprofen would be very helpful, especially for clinicians in countries where this is the only form of the drug available. Unfortunately, the intravenous preparation of ibuprofen is not easily available in North America.

REFERENCES

Lago P, Bettiol T, Salvadori S, *et al*. Safety and efficacy of ibuprofen versus indomethacin in preterm infants treated for patent ductus arteriosus: a randomised controlled trial. *Eur J Pediatr* 2002;**161**:202–7.
Supapannachart S, Limrungsikul A, Khowsathit P. Oral ibuprofen and indomethacin for treatment of patent ductus arteriosus in premature infants: a randomized trial at Ramathibodi Hospital. *J Med Assoc Thai* 2002;**85**(suppl 4):S1252–8.
Van Overmeire B, Follens I, Hartmann S, *et al*. Treatment of patent ductus arteriosus with ibuprofen. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F179–84.
Van Overmeire B, Smets K, Lecoutere D, *et al*. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;**343**:674–81.
Walia R, Ohlsson A. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants (Protocol for a Cochrane Review). In: *The Cochrane Library*, Issue 1. Oxford, 2003.

What is the use of the glass test?

Reported by
Ami Parikh, *Specialist Registrar in Paediatric A+E, St Mary's Hospital, London; simonvn@aparikh.freeserve.co.uk*
Ian Maconochie, *Consultant of Paediatric A+E, St Mary's Hospital, London*

A well 4 year old girl is seen in A+E with a rash and fever. Her parents have performed the ''glass tumbler test''and she has petechiae. You wonder how reliably this test distinguishes petechiae from other skin lesions.

Clinical bottom line

- No evidence was found to support the use of the glass tumbler test as a predictor for the diagnosis of petechiae.

Structured clinical question

In a child with a rash [patient] does a positive glass/tumbler test [test] reliably pick up petechiae [outcome]?

Search strategy and outcome

CINAHL, EMBASE, and Medline 1966–April 2003 using the OVID interface and PubMed: exp (purpuric OR purpura) OR (petechial OR petechiae) AND (tumbler OR glass). Limit to Human and English.

No relevant or irrelevant papers were found.

Commentary

The glass tumbler test is used in clinical practice and is recommended by many health organisations, including the Meningitis Research Foundation and Public Health Laboratory Service. These organistions inform parents of how to perform the glass tumbler test; by placing a glass tumbler firmly against a rash. If the parents can see the rash through the glass then the test is positive. If it is positive, parents are advised to seek medical advice immediately.[1 2]

The absence of petechiae with the glass tumbler test should not reassure parents as children with meningococcal disease (and other petechial associated infectious diseases such as group B streptococcal infection) may present without a rash or with a maculopapular rash. Relying on the absence of a petechial rash could be fatal (that is, a test result which is a false negative). The converse is also true: that all children with petechiae do not have meningococcal disease (that is, a test result which is a false positive) and therefore do not necessarily need to follow that the treatment path for meningococcal disease or other infective causes, which may be inappropriate and harmful, as the child may experiences adverse side effects of treatment. The decision for the clinician is to judge the risk of serious illness in a child with the petechiae in context of the complete clinical state of the child, and not to rely solely on this one test. More work is required to determine the sensitivity, specificity, and likelihood ratio of this oft used test.

REFERENCES

1 **Meningitis Research Foundation,** 2002. www.meningits.org.
2 PHLS website: www.phls.org.uk.