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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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

- Should we glue lip lacerations in children?
- Is nebulised tolazoline an effective treatment for persistent pulmonary hypertension of the newborn?
- How good is clinical examination at detecting a significant patent ductus arteriosus in the preterm meonate?

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### Likelihood ratios

In order to judge a diagnostic test, we need to know how accurately it rules in and rules out disease. There are a variety of terms to describe the test's properties. Some may be well known (sensitivity, specificity, predictive values), others unknown (likelihood ratio).

Likelihood ratios are the most useful way of describing a diagnostic test. They are a number which tells you how many times more likely a disease is, when you get the particular test result. For example, the presence tachypnoea (respiratory rate >60) in a 2 month old child makes the odds of pneumonia eight times more likely (that is, it has a likelihood ratio of 8). A lower respiratory rate makes the odds of pneumonia about half as likely (that is, it has a likelihood ratio of 0.55).

But what is a "good" likelihood ratio, and what is a "bad" one? As a rough guide, likelihood ratios of 1–2 are almost useless at making a diagnosis, and likelihood ratios (LRs) of 1–0.5 (that is, one half) are useless at ruling out a diagnosis. A moderate test has an LR of 2–10 (or 0.5–0.1), a good test an LR of 10–50 (or 0.1–0.02), and an excellent test an LR of >50 or <0.02.

The one difficulty with likelihood ratios is the need to apply them to odds of disease, rather than the more understandable probability of disease. (Unless you want to end up in Gambler's Anonymous, don't even try to understand odds. Ignore them, or if you need to use them, convert them into probabilities.) There is a way out of this—using the nomogram in fig 1.

(If you really want to know, you convert probabilities to odds by taking the probability (as a decimal) and call it p, and odds = p/1−p. To convert them back to probabilities, take the odd as a decimal (o) and then probability = o/1+o.)

## 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://www.cebm.net/docs.levels.htm [accessed October 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)

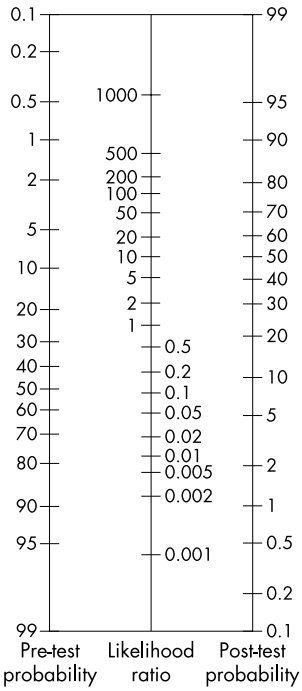


**Figure 1** Nomogram for determination of likelihood ratio (from www.cebm.net).

# Should we glue lip lacerations in children?

**Report by**

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A 7 year old boy presents to the emergency department having fallen in the playground, sustaining a laceration to his bottom lip which crosses the vermilion border. You know that the potential uses of tissue adhesive in the paediatric population are increasing, and wonder if it may be used in these circumstances instead of the traditional method of formal suturing.

## Structured clinical question

In children who have sustained a lip laceration extending through the vermilion border [patient], is tissue adhesive [intervention] better than sutures [comparison] at reducing procedural discomfort and improving cosmetic outcome [outcomes]?

## Search strategy and outcome

Medline 1966 to August 2002 using the Ovid interface (exp lacerations or exp wounds, nonpenetrating or exp facial injuries or laceration$.mp or exp wounds and injuries or wound$.mp) and (exp lip or lip$.mp or vermilion$.mp) and (exp fibrin tissue adhesive or exp tissue adhesives or tissue adhesive$.mp or $cyanoacrylate$.mp or exp cyanoacrylates or wound glue$.mp or histoacryl.mp or exp wound healing or exp suture techniques) limit to human and English.

Altogether 292 papers were found, of which only one described the proposed intervention.[1] Three other papers were found comparing tissue adhesive to sutures in paediatric patients with facial lacerations, and these have also been included in table 1.

## Commentary

Traditional teaching has been that in lacerations involving the lip, the vermilion border must be accurately approximated with a suture to ensure that healing occurs without a step. A recent systematic review[2] has outlined the benefits of using tissue adhesive as an alternative method of wound closure to sutures, and three studies have specifically looked at a comparison between tissue adhesive and sutures in paediatric facial lacerations.[3–5] These all compared tissue adhesive to sutures, and gave comparable cosmetic results with less time taken for the procedure and less pain for the child with tissue adhesive. However, lacerations of the lip were excluded from these trials. Although it is tempting to extrapolate these findings to other specific areas of wound management such as closure of lip lacerations, problems associated with this location could be anticipated, such as the child biting or licking off the glue. It should be borne in mind that there is a small but statistically significant increased rate of dehiscence with tissue adhesives compared to sutures.[2] There is only one

**Table 1** Should we glue lip lacerations in children?

| Citation | Study group | Study type (level of evidence) | Outcome | Key results | Weaknesses |
|---|---|---|---|---|---|
| de Blanco (1994) | A 10 year old boy and a 46 year old woman, both with lip lacerations | Case report (level 4) | Cosmesis at 18 days and 1 year | Wound closed with only slight scar | Simple case report, no comparison with standard, one of the patients adult |
| Quinn *et al* (1993) | 81 paediatric patients with clean facial lacerations, randomised to glue or sutures | PRCT (level 1b) | Cosmetic score at 3 months, procedural pain, time taken for procedure | No difference in cosmesis, glue faster and less painful than sutures | Lip lacerations excluded |
| Bruns *et al* (1996) | 61 paediatric patients with facial and scalp lacerations, randomised to glue or sutures | PRCT (level 1b) | Cosmetic score at 2 months, procedural pain (perceived by parents), time taken for procedure | No difference in cosmetic outcome, glue faster and less painful than sutures. Parents more likely to recommend glue to others | Lip lacerations excluded |
| Barnett *et al* (1998) | 163 paediatric patients with non-ragged lacerations, randomised to glue or sutures | PRCT (level 1b) | Cosmetic score at 3 and 12 months, procedural pain (perceived by parents, doctors, nurses, and children), time taken for procedure | Glue faster and less painful than sutures (scored by all except the child). No difference in cosmesis at 3 or 12 months | Lacerations to all body parts included except eyes and mucous membranes |

published case report supporting tissue adhesive as a method of closure in these lacerations.

**CLINICAL BOTTOM LINE**

- Pending further studies looking specifically at this problem, local advice should be followed.


**REFERENCES**

1 **de Blanco LP**. Lip suture with isobutyl cyanoacrylate. *Endod Dent Traumatol* 1994;**10**:15–18.
2 **Farion K**, Osmond MH, Hartling L, *et al*. Tissue adhesives for traumatic lacerations in children and adults. *Cochrane Database of Systematic Reviews* 2002(3):CD003326.
3 **Quinn JV**, Drzewiecki A, Li MM, *et al*. A randomized, controlled trial comparing a tissue adhesive with suturing in the repair of pediatric facial lacerations. *Ann Emerg Med* 1993;**22**:1130–5.
4 **Bruns TB**, Simon HK, McLario DJ, *et al*. Laceration repair using a tissue adhesive in a children's emergency department. *Pediatrics* 1996;**98**(4 pt 1):673–5.
5 **Barnett P**, Jarman FC, Goodge J, *et al*. Randomised trial of histoacryl blue tissue adhesive glue versus suturing in the repair of paediatric lacerations. *J Paediatr Child Health* 1998;**34**:548–50.


# Is nebulised tolazoline an effective treatment for persistent pulmonary hypertension of the newborn?


**Report by**

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You are working as a pharmacist supporting a tertiary neonatal unit. A 36/40 gestation infant is transferred from another hospital. The infant had been born by normal vaginal delivery and collapsed on the postnatal ward at 3 hours of age. The child is hypoxic despite high pressures and 100% oxygen. The diagnosis of persistent pulmonary hypertension (PPH) is suggested; intravenous tolazaline had been tried without significant improvement. Nebulised tolazaline is mentioned, and you are asked to find out more.

## Structured clinical question

In severe PPH of the newborn [patient], is nebulised tolazoline [intervention] an option when intravenous tolazoline [comparator] has failed to produce an improvement in oxygenation [outcome]?

## Search strategy and outcome

### Secondary sources

Medicines for children: information on intravenous tolazoline but not on nebulised.
Guy's formulary: no information
LTH neonatal formulary: no information.
Northern neonatal network formulary: intratracheal instillation experimental, when formulary written.

### Primary source

Medline: "tolazoline" and "nebulised/nebuliser/vapourisers/aerosols /inhalation" (two relevant studies). See table 2.

## Commentary

There is no good quality study addressing the use of nebulised tolazoline in PPH, and none addressing the use after intravenous tolazoline has failed. The only study that has been conducted to date was a case series of only 12 infants. It is difficult to attach significance to a treatment group so small. The study concluded that the endotracheal route is preferred because it is devoid of significant side effects (for example, hypotension and flushing), but it is worth noting that tolazoline is acid in solution and may cause some alveolar injury. The case report concluded that in their case the endotracheal use of tolazoline was life saving and warrants further clinical trials.

**CLINICAL BOTTOM LINE**

- Nebulised tolazaline may be effective, but no data reliably compare it to the intravenous route or other drugs.


**REFERENCES**

1 **Welch JC**, Bridson JM, Gibbs B. Endotracheal tolazoline for severe persistent pulmonary hypertension of the newborn. *Br Heart J* 1995;**73**:99–100.
2 **Parida SK**, Baker S, Kuhn R, *et al*. Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997;**17**:461–4.
3 **Meadow W**, Rudinsky B, Bell A, *et al*. Effects of nebulized nitroprusside on pulmonary and systemic hemodynamics during pulmonary hypertension in piglets. *Pediatr Res* 1998;**44**:181–6.


**Table 2** Nebulised tolazoline in persistent pulmonary hypertension of the newborn

| Citation | Study group | Study type (level of evidence) | Outcome | Key results | Comments |
|---|---|---|---|---|---|
| Welch *et al* (1995) | One infant | Retrospective case report (level 4) | Increased oxygen saturation and concomitant rise in systemic BP. Resolution of metabolic acidosis | | Tolazoline is acid in solution with pH of 4. Direct administration of an acid solution to the lungs may cause some alveolar injury |
| Parida *et al* (1997) | 12 neonates | Case series (level 3b) | Improved oxygenation, particularly sick preterm infants | Significant increase ($p<0.005$) in the mean levels of oxygen saturation and the arterial oxygen tension | Endotracheal route is preferred because it is devoid of significant side effects (e.g. hypotension and flushing) |
| Meadow *et al* (1998) | 23 piglets | Bench research (level 5) | Did not reduce pulmonary artery pressure significantly but did lower systemic arterial pressure | | Cautious extrapolation of these findings to selected clinical conditions in human infants may be warranted |

# How good is clinical examination at detecting a significant patent ductus arteriosus in the preterm neonate?

**Report by**

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A 25 week gestation infant aged 30 days has a continuous murmur and easily palpable pulses. He has already received a course of indomethacin for a "clinically diagnosed" patent ductus arteriosus (PDA). The baby is ventilator dependent. How good (or bad) is clinical examination at diagnosing a clinically important PDA?

### Structured clinical question

In a ventilator dependent neonate of very low birth weight (<1000 g) [patient], how good is clinical examination [intervention] at detecting patent ductus arteriosus [outcome]?

### Search strategy and outcome

A search string of [patent arterial duct] AND [diagnostic test] was used.

Search results

PubMed—three papers.
Cochrane database—nil.
SUMSearch—nil other than PubMed articles.
Search done independently by DU and RN retrieved same three articles. See table 3.

### Commentary

PDA is common in preterm babies. The EPICure study[4] documented the prevalence as 65% in babies born at less than 26 weeks who survive to discharge. However, the methods for diagnosing a PDA in this study were not specified. Therefore, the pretest probability of a ventilated preterm infant having a PDA is high.

In the study by Davis and colleagues,[1] a high percentage of patients with a PDA had no murmur. Bounding pulses were also a poor independent predictor for the presence of a PDA. We can also calculate post-test probability for patent ductus arteriosus using the likelihood ratios (LRs) from this study. For presence of a murmur alone, if we assume a pretest probability of 65%,[4] and positive LR of 3.23, then our post-test probability is increased to 86%. However, if no murmur is present and negative LR is 0.67, post-test probability falls only to 55%.

For an increased pulse volume, with a pretest probability of 65%, post-test probability is increased to 75% when there are bounding pulses but falls only to 59% when bounding pulses are absent. Therefore echocardiography is required to confirm or refute a diagnosis of PDA.

The paper by Skelton and colleagues[2] evaluated signs over a period of several days. The presence of a murmur was highly specific, but poorly sensitive in diagnosing patent ductus arteriosus. Hence, a murmur heard in a preterm infant is likely to be due to patent ductus arteriosus; however absence of a murmur does not exclude a PDA. Therefore to be confident of the diagnosis, echocardiography is essential.

The results of the Kupferschmid *et al* paper[3] were less valid, as they compared a group of 29 PDA patients with a control group, of whom 11 were patients from the original group that had subsequently undergone PDA ligation. The presence of a thoracotomy scar would preclude blinding. Twenty per cent of patients with a PDA had normal heart sounds and 10% had normal pulses on assessment. No gold standard was applied, with definitive diagnosis of PDA made from either operative, postmortem, or aortography findings.

**Table 3** Detection of patent ductus arteriosus in the preterm neonate

| Citation | Study group | Level of evidence | Outcome | Key results | Comments |
|---|---|---|---|---|---|
| Davis *et al* (1995) | 100 babies <1750g studied between day 3 and day 7 of life | Level 1b | Detection of PDA by clinical examination versus echocardiography (gold standard) | *Murmur*<br>LR+ 3.23 (CI 1.2, 10)<br>LR– 0.67 (CI 0.53, 0.93)<br>*Bounding pulses*<br>LR+ 1.65 (CI 0.79, 3.53)<br>LR– 0.77 (CI 0.48, 1.16) | Clinical signs poor predictors of PDA |
| Skelton *et al* (1994) | 55 babies <1500g studied in the first 7 days of life | Level 1b | Detection of PDA by clinical examination versus echocardiography (gold standard) | *Murmur*<br>LR+ ranges from 3 to 14 in first 7 days (CI 0.8–5, 9.1–22)<br>LR– ranges from 0 to 0.8 in first 5 days (CI 0.1–0.5, 0.8–1.2)<br>*Bounding pulses*<br>LR+ ranges from 0.3 to 6 in first 7 days (CI 0–3, 2–12)<br>LR– ranges from 0 to 1.3 in first 5 days (CI 0.1–1.0, 1–1.7) | Clinical signs poor at detecting PDA in first 4 days of life. Echocardiography is required for reliable early diagnosis of PDA |
| Kupferschmid *et al* (1988) | 47 babies<br>1. Cases: 29 with PDA<br>2. Controls: 29 without PDA of whom 11 were drawn from group 1 following duct ligation | Level 4 | Detection of PDA by clinical examination, echo and Doppler. No gold standard | *Murmur*<br>80% sensitivity (95% CI 60, 92)<br>*Bounding pulses*<br>90% sensitivity (CI 73, 98)<br>Unable to calculate LRs as specificity not stated | Concerns re blinding in view of how controls were obtained. Clinical signs are poor predictor of PDA |

Post-test probability suggests that clinical evaluation of PDA either by auscultation or by palpation of pulses is of limited value. Echocardiography is the method of choice for diagnosing a patent arterial duct.

**CLINICAL BOTTOM LINE**

- Clinical evaluation of PDA, either by auscultation or by palpation of pulses, is of limited value (with likelihood ratios between 0.3 and 6).
- In the extremely low birthweight neonate, Doppler flow echocardiography is required to confidently rule in or rule out the diagnosis of PDA.

## REFERENCES


1 **Davis P**, Turner-Gomes S, Cunningham K, *et al*. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. *Arch Pediatr Adolesc* 1995;**149**:1136–41.
2 **Skelton R**, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. *J Pediatr Child Health* 1994;**30**:406–11.
3 **Kupferschmid C**, Lang D, Pohlandt F. Sensitivity, specificity and predictive value of clinical findings, m-mode echocardiography and continuous wave Doppler sonography in the diagnosis of symptomatic patent ductus arteriosus in preterm infants. *Eur J Pediatr* 1988;**147**:279–82.
4 **Costeloe K**, Hennessy E, Gibson AT, *et al*. The EPICure study: outcomes to discharge from hospital for infants born at the threshold of viability. *Paediatrics* 2000;**106**:659–71.