Towards evidence based medicine for paediatricians

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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. They are based on an original format from the *Journal of Accident and Emergency Medicine*.²

A word of warning. These best evidence topic summaries (BETs) are not systematic reviews, though 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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.

Each topic follows the same format. A description of the clinical setting is followed by a structured clinical question. (These aid in focusing the mind, assisting searching,³ and gaining answers.⁴) 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.⁵ 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 Sackett⁶ and Moyer⁷ may help. A commentary is provided to pull the information together, and for accessibility, a box provides the clinical bottom lines.

Readers wishing to submit their own questions—with best evidence answers—are encouraged to read the Instructions for Authors at <http://www.archdischild.com>. Three topics are covered in this issue of the journal.

- ▶ Nitric oxide in preterm babies
- ▶ Partial plasma exchange transfusion in polycythaemic neonates
- ▶ Phenytoin in traumatic brain injury

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- 5 <http://cebmlr2.ox.ac.uk/docs/levels.htm>
- 6 **Sackett DL**, Starus S, Richardson WS, *et al*. *Evidence-based medicine. How to practice and teach EBM*. San Diego: Harcourt-Brace, 2000.
- 7 **Moyer VA**, Elliott EJ, Davis RL, *et al*, eds. *Evidence based pediatrics and child health, Issue 1*. London: BMJ Books, 2000.

Nitric oxide in preterm babies

Report by Richard Nicholl, Consultant Neonatologist, Northwick Park Hospital

A 25 week gestation male infant, birth weight 520 g, is transferred ex utero to your neonatal unit for intensive care. On day 19 he remains ventilator dependent and is hypoxic on 60-95% oxygen. The oxygenation index (OI; a measure of respiratory failure) is 18. Chest x ray shows clear lung fields. Echocardiography by a senior paediatric cardiologist shows evidence of pulmonary hypertension. In view of these findings it is felt that a pulmonary vasodilator may help. You discuss entering the INNOVO trial (a multicentre

Numbers needed to treat

The "NNT" (number needed to treat) is seen as the hallmark "statistic" in evidence based medicine. But what is it, and how should it be interpreted?

The NNT is "the number of patients needed to treat with A (compared with B) to prevent one defined outcome in a specified time period". It is the inverse of the risk difference between the two treatments. (For example, if 5% of children with croup who receive steroids are admitted, and 25% of those who receive placebo are admitted, the risk difference is 20%, so the NNT is 5.) Apply this result with caution! If the NNT is 5, this means that for every five children treated with steroid, one extra admission is prevented. Of the children you see, 75% of them would have gone home anyway.

"Numbers needed to treat" also relate to a specific dichotomous outcome. It's common sense to check that the outcome measures are the same if one is comparing NNTs, but two further issues must be considered. Firstly, the effect of time. One croup trial may have used admission in the following week, and another admission within four hours. Secondly, baseline risks vary between studies. If the croup study was done in the community, perhaps only 10% of the untreated croup patients would have been admitted. Assuming the steroid was equally effective, and reduced the risk of hospitalisation by four fifths, the treated admission rate would be 2%. This gives an NNT of 13.

So the NNT does not reflect the observed benefit of a treatment in practice, but how it compares with another treatment (often placebo). The NNT tells you about one particular population, with a particular degree of baseline risk over a particular period of time. Comparing NNTs requires some form of adjustment for this.

What the NNT does give is a common shorthand. For example, if the NNT to give good outcome, and the NNT to produce side effects can be calculated, the explicit weighing of harm and benefit becomes much clearer.

Table 1

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Kinsella <i>et al</i> (1999)	80 preterm babies, <34 wk, randomised to 5 ppm inNO or control	Double blind RCT, single centre (level 1b)	Survival to discharge	RR 1.11 95% CI 0.70–1.8	Exp group had improved PaO ₂ at 60 min; study underpowered
The Franco-Belgium Collaborative NO trial Group (1999)	204 preterm babies, randomised to 10 ppm inNO or control	Open, multicentre, RCT (level 1b)	OI at 2 h	Median 8.4 (inNO) v 12.4 (control); p=0.005 Greatest in near term infants	Study underpowered; baseline OI higher in the experimental group
Subhedar <i>et al</i> (1997)	42 preterm babies (<32 wk) randomised to inNO alone; dexamethasone alone; both; neither	Open RCT (level 1b)	Death before discharge and/or CLD	RR 1.05 95% CI 0.84–1.25 for inNO v controls	Neither treatment prevented CLD or death
Skimming (1997)	23 preterms randomised to either 5 or 20ppm inNO	Open RCT (level 1b)	Arterial blood oxygen tension, 15 min after intervention	Equal increases in primary outcome, both groups	Short term physiological study; no control group

randomised controlled trial of addition of inhaled nitric oxide (inNO) to babies with severe respiratory failure) with the parents, who agree; the baby is entered into the control (no addition of inNO) arm. In spite of this, parents ask for “everything” (including inNO) to be tried. Reluctantly you agree and inNO is administered as per the trial protocol (you inform the trial coordinators). The baby does not improve, and dies 24 hours later. Was it reasonable to administer inNO to this baby?

Structured clinical question

In ventilated preterm babies with pulmonary hypertension and hypoxia [patient], does addition of inhaled nitric oxide [intervention] reduce mortality [outcome]?

Search strategy and outcome

Using Cochrane Library: 1 relevant. Using PubMed—“nitric oxide” AND “premature” AND “randomised clinical trial”: 5 randomised trials. See table 1.

Commentary

None of the above studies is able to answer our original question. The largest studies were under powered and failed to show important benefits for inNO in preterm babies. The smaller studies showed short term physiological changes; e.g. Subhedar *et al*: transient fall in OI with 5 ppm inNO; Skimming *et al*: equal increases in oxygen tension after 15 min of either 5 or 20 ppm inNO.

The possible longer term side effects of inNO are not known. In spite of this, inNO is being routinely used in many UK neonatal units, without the safeguards implicit in participation in a clinical trial (Safeguarding informed parental involvement in clinical research involving newborn babies and infants. A Position Statement. Royal College of Paediatrics and Child Health, December 1999).

(See also Cochrane Library Reviewers’ conclusions—which do not contain the two largest studies above, at time of writing, as they are too recent).

► CLINICAL BOTTOM LINE

- Preterm infants should not be treated with inhaled nitric oxide outside prospective, randomised controlled trials.
- Long term follow up of these babies is needed.

Kinsella JP, Walsh WF, Bose CL, *et al*. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial. *Lancet* 1999;**354**:1061–5.

The Franco-Belgium Collaborative NO trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomised controlled trial. *Lancet* 1999;**354**:1066–71.

Subhedar NV, Shaw NJ. Changes in oxygenation and pulmonary haemodynamics in preterm infants treated with inhaled nitric oxide. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F191–7.

Subhedar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1997;**77**:F185–90.

Skimming JW, Bender KA, Hutchinson AA, Drummond WH. Nitric oxide inhalation in infants with respiratory distress syndrome. *J Pediatr* 1997;**130**:225–30.

Partial plasma exchange transfusion in polycythaemic neonates

Report by Tammy Rothenberg, Department of Gastroenterology, Great Ormond Street Hospital

You are a neonatal junior doctor looking after the special care nursery. You process a capillary blood sample taken on the morning blood round by someone who has now gone home, and find the haematocrit to be high at 69%. You go back to the baby and find the child to be term, of low birth weight, and admitted to the special care nursery because of low Apgars the previous day. He has not been feeding too well, but the neonatal nurses are not otherwise concerned. He is normal on examination, and his venous haematocrit comes back at 68%. Does this baby need a partial plasma exchange transfusion (PPET)?

Structured clinical question

In an asymptomatic neonate with an incidental finding of raised venous haematocrit [patient], does treatment with a partial plasma exchange transfusion [intervention] reduce adverse neurological outcome [outcome]?

Search strategy and outcome

Using the Cochrane Controlled Trials Register—“Polycythaemia”. Verified using Medline—“polycythaemia”, “neonate”, AND “RCT filter”. Six papers identified, of which one irrelevant and one of insufficient quality. See table 2.

Commentary

The research papers all use hyperviscosity rather than polycythaemia as the basis for their studies. The test for this is

Table 2

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Bada <i>et al</i> (1992)	28 neonates screening cord blood haematocrit, and found to have both arterial haematocrit $\geq 63\%$ with hyperviscosity, and asymptomatic Randomised to PPET or symptomatic care	RCT (level 1b)	Mental development index/IQ Mental retardation rate	Mean score in treated group 85 v observed 88; difference -3 (95% CI -19 to +13) Higher borderline retardation rate in treated group (66% v 45%; ARR = 0.21 (95% CI -0.21 to 0.63)	Mean 27.5 mth follow up, assessors blind to neonatal course 71% follow up rate
Black <i>et al</i> (1985)	93 neonates selected by: admission to nursery at 4–6 h of age, screened by heel prick testing, and found to have both venous polycythaemia (HCT $\geq 65\%$) and hyperviscosity, includes symptomatic and asymptomatic Randomised to PPET or symptomatic care	RCT (level 1b)	Mental delay rate Motor delay rate Neurological diagnosis rate	Reduced by PPET (18% v 13%); “not significant” (numbers not given) Reduced by PPET (19% v 35%); “not significant” (numbers not given) Reduced by PPET (25% v 55%); $p < 0.05$	2 years follow up 65% follow up rate Includes 2 deaths in observed group, one of head trauma and one of hepatitis
Goldberg <i>et al</i> (1982)	20 neonates, selected by: screening heel prick on all babies, result $\geq 68\%$, and hyperviscous on venous blood, excludes neurologically symptomatic Randomised to PPET or symptomatic care	RCT (level 1b)	Bayley mental development index Bayley psychomotor development index Abnormal neurological findings Abnormal postural reflexes	Mean difference 2.6 (95% CI -16 to 21) (control score 112) Mean difference -0.8 (95% CI -13 to 15) (control score 108) 1/6 of treatment group, 5/10 observed group, NNT = 3 (95% CI -10 to 1) 6/10 in treatment group, 0/6 in observed group, NNT = 2 (95% CI 1 to 3)	8 months 80%
van der Elst <i>et al</i> (1980)	49 neonates selected by: appearance of polycythaemia, central haematocrit $\geq 65\%$, and no symptoms, or mildly symptomatic* Randomised to PPET or symptomatic care	RCT (level 1b)	Developmental score Neurological examination	“No difference” “No difference” (normal in all)	8 months follow up 86% follow up one death (NEC) in treatment group

*“Minor signs” defined as lethargy, tremulousness, irritability, peripheral cyanosis, vomiting, and poor feeding.

not routinely available, and so in the clinical setting, polycythaemia is used as a marker for hyperviscosity. Hyperviscosity is the increased internal friction of blood. It varies according to the flow rate; it is in the capillaries, where the flow rate is low, that the hyperviscosity is thought to contribute to reduced tissue perfusion. Red cell concentration (haematocrit) contributes significantly to viscosity; Bada *et al* found a consistent correlation between the two ($r = 0.5$, $p < 0.001$).

Neonatal polycythaemia is associated with adverse neurological outcome. All papers in the table included a control group of non-polycythaemic or non-hyperviscous infants. The group of infants in the Black *et al* study showed a significant overall risk of mild developmental delay; this risk was greater than the modest treatment effect, compared with infants controlled for gestational age, birth weight, but not for perinatal risk factors (see table 2A).

The Bada *et al* study matched the control group for gestational age, birth weight, and perinatal risk factors of fetal distress or asphyxia, pre-eclampsia, and maternal diabetes.

Table 2A

2 year follow up	All hyperviscous infants	Control	p value
Mental delay	16%	10%	NS
Motor delay	27%	2%	<0.001
Neurological diagnosis	40%	9%	<0.001

Regression analysis was performed to determine the effects of these risk factors on outcome. The risk of adverse neurological outcome was more strongly predicted by perinatal risk factors than the presence of hyperviscosity.

It is notable that there was no abnormal neurology in the infants studied at eight months follow up by van der Elst *et al*, which may be a result of the type of patients included, the small numbers of patients, or the relatively short follow up period. The subjects of the Black *et al* study included some who were neurologically normal at 1 year, but had developed signs by 2 years of age. However, the relatively low follow up rate (65% for those randomised, 51% for control infants) makes the findings tentative at best. Similarly, although the Goldberg *et al* study has 80% follow up of the 20 patients, only 6/10 of the observation group were studied, in contrast to 10/10 of the treatment group.

It is important to assess whether these patients are comparable to the clinical scenario. Only the van der Elst patients were selected on clinical grounds (“appearing polycythaemic”), the other patients being selected by a screening process. The other factor that makes the van der Elst *et al* group of patients comparable in particular to this scenario is that the infants included those who had “minor signs”, defined as lethargy, irritability, peripheral cyanosis, vomiting, and poor feeding.

► CLINICAL BOTTOM LINE

- Polycythaemia is a risk factor for later neurological abnormality.
- Partial plasma exchange transfusion has no clear long term benefit in asymptomatic polycythaemia or hyperviscosity, though evidence either way is weak and inconsistent.

Bada HS, Korones SB, Pourcyrus M, *et al.* Asymptomatic syndrome of polycythaemic hyperviscosity: effect of partial plasma exchange transfusion. *J Pediatr* 1992;120:579–85.

Black VD, Lubchenko LO, Koops BL, *et al.* Neonatal hyperviscosity: randomized study of effect of partial plasma exchange transfusion on long-term outcome. *Pediatrics* 1985;75:1048–53.

Goldberg K, Wirth FH, Hathaway WE, *et al.* Neonatal hyperviscosity II. Effect of partial plasma exchange transfusion. *Pediatrics* 1982;69:419–25.

Malon AF, de V Heese H. The management of polycythaemia in the newborn infant. *Early Hum Dev* 1980;4:393–403.

Phenytoin in traumatic brain injury

Report by Elizabeth A Hunt, PICU Fellow at Johns Hopkins Hospital in Baltimore

A 12 year old boy is admitted to the paediatric intensive care unit after a motor vehicle collision, where he sustained a severe closed head injury. He lost consciousness at the scene and was intubated in the emergency department for a Glasgow Coma Score of 8 and no gag reflex. The boy has no history of seizure activity in the past or at the scene. Your local “Traumatic Brain Injury Protocol” recommends that he receive phenytoin for seizure prophylaxis. You have recently cared for a child who nearly died from phenytoin hypersensitivity syndrome and would like to know if there is a good indication for the drug.

Structured clinical question

In a child with a traumatic brain injury [patient] does phenytoin prophylaxis [intervention] prevent subsequent seizures and/or improve neurological outcome [outcome]?

Search strategy and outcome

Secondary sources—none since 1972.

Systematic reviews—two, performed by same authors: Cochrane Library (Issue 3, 2001) and Evidence-Based Medicine (v3, 1998; initially published in *J Neurol Neurosurg Psychiatry*, 1998); reviewed use of “anti-epileptic drugs”, not just phenytoin.

Primary research—PubMed query using MeSH subject headings: “Craniocerebral Trauma” AND “Epilepsy, Post-Traumatic” AND “phenytoin” and filter “therapy”.

Search results—52 articles; after “therapy” filter: 4 relevant (1 not placebo controlled, blinded or readily available, therefore not included here, but is included in systematic reviews). See table 3.

Commentary

In addition to determining the potential efficacy of phenytoin as prevention for post-traumatic epilepsy, there are other important outcomes to bear in mind. Although anti-epileptics appear to decrease the rate of early seizures, this has not been shown to result in a lower rate of post-traumatic epilepsy, mortality, or improved cognitive outcome.^{2–4} In addition, multiple studies have shown that continued use of phenytoin in this population is associated with “negative effects on cognitive performance”.⁵

One must also consider that phenytoin is not a benign drug. Although studies have not revealed a high rate of side effects

Table 3

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Schierhout <i>et al</i> (2001)	6 controlled trials, 1218 randomised patients; includes studies with both adults and children, some studies used other antiepileptics than phenytoin	Systematic review (level 1a)	Early seizures (in 1st 7 days post-injury) Late seizures (after 1st 7 days post-injury) Mortality Neurologic disability, (Glasgow Outcome Score)	RR for early seizure prevention 0.34 (CI 0.21–0.54); NNT=10; No? mortality, RR=1.15 (CI 0.89–1.51); No ? in death and neurologic disability RR= 0.96 (CI 0.72–1.26); No ? in late seizures Pooled RR =1.28 (CI 0.90–1.81)	Early seizure prevention values represent 4 studies with phenytoin and 2 with other agents Studies very heterogeneous in relation to late seizure outcome
McQueen <i>et al</i> (1983)	164 patients ages 5 to 65 with serious head injuries (pts with seizures 1st wk post injury excluded)	Double blind RCT (level 1b)	Late seizures, overall mortality, skin rashes	No significant differences Late seizure ARR = –0.77% (CI –9.59 to +8.04) Mortality ARR = –3.45% (CI –9.56 to +2.66) Rash ARR = –4.7% (CI –10.32 to +0.91)	Loss to follow up at 2 years 1.2% (5% if include deaths) Authors’ note: based on low incidence of events, future trials will have to be ~6x larger than theirs to detect an effect
Young <i>et al</i> (1983)	41 head injured children; (total study 244 pts, adult data published separately with similar results)	Double blind RCT (level 2b)	(Early seizures; data not published in this study, was collected for total study) Late seizures Overall mortality	No significant differences Late seizures ARR = –5.75% (CI –23.16 to +11.66) Mortality = 4.55% (CI –14.88 to +23.88)	Loss to follow up at 2 years 26% for overall study For children (1 withdrawn, 4 deaths in first wk not included in analysis of final 41 pts), otherwise no loss to follow up
Temkin <i>et al</i> (1990)	404 patients with serious head trauma, 16 years of age and older	Double blind RCT (level 1b for early seizure outcome, but for late seizure outcome large loss to follow up in both groups at 2 years, thus level 2b)	Early seizures (in 1st wk post-injury) Late seizures (from day 8 to the end of the year) Overall mortality, skin rashes	3.6% in treatment arm, 14.2% placebo, RR=0.27 (CI 0.12–0.62) No significant difference; 21.5% treatment, 15.7% placebo RR=1.2 (CI 0.71–2.02) No significant difference Mortality ARR = –2.64% (CI –10.74 to +5.27) Rash ARR = –3.35% (CI –9.27% to 2.58)	24% loss to follow up at 24 months (22.5% in treatment group, 25% in placebo group)

in patients treated with phenytoin for one week post-injury, physicians must still be aware of the potential for not only serious but potentially fatal reactions to the drug. A search of the literature for adverse reactions to prophylactic phenytoin in head injured patients yielded case reports of intravenous site reactions,⁶ exfoliative dermatitis,⁷ granulocytopenia,⁸ and transient hemiparesis.⁹ In other patient populations, phenytoin has been associated with permanent B cell immunodeficiency¹⁰ and fatal phenytoin hypersensitivity syndrome.¹¹ There have also been multiple publications which show that total phenytoin concentrations can be normal in a trauma patient, yet be associated with high free, unbound concentrations because of low albumin. This may be associated with a higher rate of side effects at normal “therapeutic” concentrations.¹²

Recently, a consensus guideline was published stating that “the routine use of seizure prophylaxis later than 1 week following head injury is not recommended”.¹³ The guideline recommends using a risk-benefit analysis to decide whether phenytoin or carbamazepine should be considered for high risk patients in the first week post-injury.

► CLINICAL BOTTOM LINE

- In the first seven days after serious head injury, phenytoin does prevent seizures in some patients (NNT = 10) but has not been shown to decrease mortality or post-traumatic epilepsy. For high risk patients, a physician must weigh the potential risks and benefits before making a decision.
- If phenytoin is used in trauma patients, measure free, “unbound” phenytoin concentrations to avoid toxicity.

- There is currently no indication for prophylactic phenytoin beyond the first week post head injury.

- 1 Schierhout, Roberts I. Anti-epileptic drugs for preventing seizures following acute traumatic brain injury. *The Cochrane Library* 2001;**3**.
- 2 McQueen J, Blackwood D, Harris P, *et al*. Low risk of late post-traumatic seizures following severe head injury: implications for clinical trials of prophylaxis. *J Neurol Neurosurg Psychiatry* 1983;**46**:899–904.
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- 8 Gabl M, Kostron H. Diphenylhydantoin induced granulocytopenia following seizure prophylaxis after a depressed skull fracture. *Zentralbl Neurochir* 1986;**47**:339–41.
- 9 Sandyk R. Transient hemiparesis caused by phenytoin toxicity. A case report. *S Afr Med J* 1983;**64**:493.
- 10 Guerra I, Fawcett W, Redmon A, *et al*. Permanent intrinsic B cell immunodeficiency caused by phenytoin hypersensitivity. *J Allergy Clin Immunol* 1986;**77**:603–7.
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- 13 The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Role of antiseizure prophylaxis following head injury. *J Neurotrauma* 2000;**17**:549–53.