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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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://cebim.jr2.ox.ac.uk/docs/levels.htm>
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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—“polycythemia”, “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