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. 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. 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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, and gaining answers.) 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. 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 and Mayer 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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REFERENCES

5. http://cebm.jr2.ox.ac.uk/docs/levels.htm
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**


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.


Table 1

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinsella et al [1999]</td>
<td>80 preterm babies, &lt;34 wk</td>
<td>Double blind RCT, single centre (level 1b)</td>
<td>Survival to discharge</td>
<td>RR 1.11 95% CI 0.70–1.8</td>
<td>Exp group had improved PaO₂ at 60 min; study underpowered</td>
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<tr>
<td>The Franco-Belgium Collaborative NO trial Group (1999)</td>
<td>204 preterm babies, randomised to 10 ppm inNO or control</td>
<td>Open, multicentre, RCT (level 1b)</td>
<td>OI at 2 h</td>
<td>Median 8.4 (inNO) v 12.4 (control), p=0.005 Greatest in near term infants</td>
<td>Study underpowered; baseline OI higher in the experimental group</td>
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<td>Subhedar et al [1997]</td>
<td>42 preterm babies (&lt;32 wk</td>
<td>Open RCT (level 1b)</td>
<td>Death before discharge and/or CLD</td>
<td>RR 1.05 95% CI 0.84–1.25 for inNO v controls</td>
<td>Neither treatment prevented CLD or death</td>
</tr>
<tr>
<td>Skimming (1997)</td>
<td>23 preterms randomised to either 5 or 20ppm inNO</td>
<td>Open RCT (level 1b)</td>
<td>Arterial blood oxygen tension, 15 min after intervention</td>
<td>Equal increases in primary outcome, both groups</td>
<td>Short term physiological study; no control group</td>
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</tbody>
</table>


Skimming JW, Bender KA, Hutchinson AA, Drummond WH. Nitric oxide inhalation in infants with respiratory distress syndrome. J Pediatr 1997; 130:223–30

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...
Partial plasma exchange transfusion has no clear long-term benefit in asymptomatic polycythaemia or hyperviscosity, though evidence either way is weak and inconsistent.
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: “Cranioencebral 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. In addition, multiple studies have shown that continued use of phenytoin in this population is associated with “negative effects on cognitive performance”.

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

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<td>Schierhout et al (2001)</td>
<td>6 controlled trials, 1218 randomised patients, includes studies with both adults and children. Some studies used other antiepileptics than phenytoin.</td>
<td>Systematic review (level 1a)</td>
<td>Early seizures (in 1st 7 days post-injury). Late seizures (after 1st 7 days post-injury). Mortality. Neurologic disability. (Glasgow Outcome Score).</td>
<td>RR for early seizure prevention 0.34 (CI 0.21–0.54). NNT=10. No difference in mortality, RR=1.15 (CI 0.89–1.51). No significant differences in death and neurologic disability. (RR=0.96 CI 0.72–1.26). No significant differences in late seizures. Pooled RR = 1.28 (CI 0.90–1.81).</td>
<td>Early seizure prevention values represent 4 studies with phenytoin and 2 with other agents. Studies very heterogeneous in relation to late seizure outcome.</td>
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<td>McQueen et al (1983)</td>
<td>164 patients ages 5 to 65 with serious head injuries. Pts with seizures 1st wk post injury excluded.</td>
<td>Double blind RCT (level 1b)</td>
<td>Late seizures, overall mortality, skin rashes.</td>
<td>No significant differences in late seizure ARR = −0.77% (CI −9.56 to +11.66). Mortality ARR = −3.45% (CI −9.56 to +2.66). Rash ARR = −4.7% (CI −10.32 to +0.91).</td>
<td>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 much larger than theirs to detect an effect.</td>
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<td>Young et al (1983)</td>
<td>41 head injured children; total study 244 pts, adult data published separately with similar results.</td>
<td>Double blind RCT (level 2b)</td>
<td>Early seizures; data not published in this study, was collected for total study. Late seizures. Overall mortality.</td>
<td>No significant differences in late seizures ARR = −5.75% (CI −23.16 to +11.66). Mortality ARR = 4.55% (CI −14.88 to +23.88).</td>
<td>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.</td>
</tr>
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<td>Temkin et al (1990)</td>
<td>404 patients with serious head trauma, 16 years of age and older.</td>
<td>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.</td>
<td>Early seizures (in 1st wk post-injury). Late seizures (from day 8 to the end of the year). Overall mortality, skin rashes.</td>
<td>No significant differences in late seizures ARR = −21.5% (CI −10.74 to +5.27). Rash ARR = −23.3% (CI −9.27 to +2.58).</td>
<td>24% loss to follow up at 24 months (22.5% in treatment group, 25% in placebo group).</td>
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</table>
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, exfoliative dermatitis, granulocytopenia, and transient hemiparesis. In other patient populations, phenytoin has been associated with permanent B cell immunodeficiency and fatal phenytoin hypersensitivity syndrome. 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. Recently, a consensus guideline was published stating that “the routine use of seizure prophylaxis later than 1 week following head injury is not recommended.” 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.