ARCHIMEDES

Towards evidence based medicine for paediatricians

Edited by Bob Phillips

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. 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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, 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 Moyer 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 linked to the original article when they are available.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:
• What is the role of plain abdominal radiograph in the diagnosis of intussusception?
• What is the significance of headache following head injury?
• Is nebulised salbutamol indicated in bronchiolitis?
• Are oral steroids beneficial in bronchiolitis?

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.
• Do oral antihistamines stop the itch of atopic dermatitis?
• Is elective high frequency oscillatory ventilation better than conventional mechanical ventilation in very low birth weight infants?
• Can surfactant cure babies with severe bronchiolitis?

Systematic reviews and meta-analysis

Systematic reviews of healthcare topics are seen by some as the “Holy Grail” of evidence based medicine. Just like the Holy Grail, there are a number of myths around systematic reviews, how they differ from a meta-analysis, and how they can be interpreted.

“Systematic reviews are the same as meta-analysis”

A systematic review is a study performed on previous research. It follows a simple structure: the setting of a focused question, unbiased collection of the best evidence to answer that question, appraisal of those studies found, and an overview of that information in context.

Meta-analysis is a family of statistical techniques that combine the results of different studies into a single summary result. The underlying presumption is that all the studies are really telling us the same answer, and that by chance the results have differed. Combining them as though they were all one study makes us able to give a more precise estimate of the result.

A systematic review might, if the data appear similar, use meta-analysis to produce an overall result. On the other hand, the review might favour giving a narrative conclusion. What’s also clear is that if a meta-analysis is performed without a systematic review, there is an increased risk of an incorrect result.

“Systematic reviews are of randomised controlled trials”

Systematic reviews have been largely of treatments. (The Cochrane database is almost all reviews of interventions.) In these reviews, the basic study design is a randomised controlled trial, as this is the least biased way of assessing the effects of an intervention. There are an emerging number of systematic reviews of other questions—diagnostic tests, prognostic variables, and even aetiological elements like genetic polymorphisms have been subject to this process.

“Systematic review is better than any other study”

Just like any other study, systematic reviews need critically appraising and their results interpreting in the context of their weaknesses. Even a well performed systematic review does not always give us the “right” answer: what it gives us is the current best guess. We should always be questioning, revisiting, and reassessing our activity in the light of better evidence as it emerges.

REFERENCES

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Do oral antihistamines stop the itch of atopic dermatitis?

Report by
Susie Dimson, Registrar, Newham General Hospital, UK
Cham Nanayakkara, Registrar, Hammersmith Hospital, UK

You are a paediatric SHO, on a night shift. You are called to the ward to see a 6 year old girl, who cannot get to sleep because her eczema is too itchy. The nurses want you to prescribe an antihistamine, but you doubt the efficacy of this treatment. As it is a surprisingly quiet shift, you go off to do a literature search.

Structured clinical question
In children with atopic eczema [patient], does the use of oral antihistamines [intervention] reduce the incidence of itching [outcome]?

Table 1 Oral antihistamines in atopic dermatitis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Munday et al</td>
<td>155 paediatric patients with atopic dermatitis causing nocturnal itching and scratching, randomised to placebo or chlorpheniramine. Age 1–12 years</td>
<td>RCT, double blind (level 1b)</td>
<td>Cessation of nocturnal itching and scratching compared to any itching symptoms at all. Assessed over 4 week period with itching scores and diary cards</td>
<td>1–5 years: small reduction in symptoms in children age 1–5 years, but not statistically significant. ARR 18% (95% CI 0.05 to 0.14) 6–12 years: no difference in 6–12 years. ARR 12% (95% CI 0.05 to 0.11)</td>
<td>Unclear how patients randomised and concealment of group. 4 patients not accounted for in final data analysis. Patients from different centres had differing intensity of treatment prior to study. Unvalidated 5 point rating scale</td>
</tr>
<tr>
<td>La Rosa et al</td>
<td>22 children with atopic dermatitis, randomised to placebo or cetirizine. Age 6–12 years</td>
<td>RCT, double blind (level 1b)</td>
<td>Decrease in pruritus. Assessed over 4 and 8 week period with scoring system and clinical assessment</td>
<td>Citirizine reduced symptoms more than placebo over first week, but no percentage reduction given (p&lt;0.02). Pruritus scores the same at 4 week intervals</td>
<td>No data on randomisation details and concealment. Small numbers. Not specified who performed clinical assessments. Results not specified, no confidence intervals, arbitrary scales on graphs for intensity of pruritus. Percentage improvement figures were not given for both placebo and treatment groups, so not comparable</td>
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</tbody>
</table>

Search strategy and outcome

Cochrane—none.
PubMed: search words—“atopic dermatitis” AND “chlorpheniramine” OR “antihistamines”.
Limits—English, human, child <18 years.

SUMSearch—one paper, already retrieved by Pubmed.
See table 1.

Commentary

Current teaching in the treatment of atopic dermatitis incorporates the use of oral antihistamines to eliminate itch. These are thought to work on the H1 receptor to decrease histamine release and therefore eliminate itch. In addition the older antihistamines have a sedative effect, encouraging a complete night’s sleep.

The study by La Rosa et al was a small study, with only 12 patients per group. It is therefore difficult to establish the statistical significance of their results. The authors did not provide the raw data, instead referring to isolated percentage changes which were difficult to interpret.

The Munday et al study was a more comprehensive study, with larger numbers. However, some of the patients were recruited from Poland and they had not received optimal eczema therapy prior to the onset of the trial. These patients then received steroid and emollient creams, so their improvement might have been a result of the improved eczema management, rather then the antihistamines. Despite this, there was still no difference between the two groups.

There are no good quality studies investigating the efficacy of oral antihistamines. Neither of the two studies reviewed showed any significant reduction in symptoms, nor did they show a statistical difference. We feel that the case was not
proven either way for the use of antihistamines, but due to the flaws pointed out above, further trials are needed in children.

REFERENCES

Is elective high frequency oscillatory ventilation better than conventional mechanical ventilation in very low birth weight infants?

Report by
Sachin Shah, Fellow, Hospital for Sick Children and University of Toronto, Toronto, Canada

A 26 week infant is about to be delivered by emergency caesarean section to a mother with placental abruption and fetal distress. No antenatal steroids have been administered to the mother. You are called to attend the delivery. You are setting up the equipment when the respiratory therapist suggests that we should use high frequency oscillatory ventilation (HFOV) as primary mode of ventilation. He also cites few articles suggesting benefit of high volume strategy HFOV over conventional ventilation (CV). You wonder if there is enough evidence to support the intervention.

Structured clinical question

In very low birth infants with respiratory distress syndrome [patient], is elective high frequency oscillatory ventilation using high volume strategy [intervention] better than conventional mechanical ventilation [comparison] in decreasing chronic lung disease or mortality at 36 weeks corrected gestational age [outcome]?

Search strategy and outcome


Cochrane: “high frequency ventilation” AND “infant, newborn” OR “infant, preterm”. Medline: “high frequency ventilation” and “infant, newborn” OR “infant, preterm” AND “chronic lung disease OR bronchopulmonary dysplasia” AND “randomised clinical trial”.

Overall, 13 RCTs of HFOV versus CV were found in the search, of which eight met the eligibility criteria of the Cochrane review and are included in the review. Two RCTs have been published since the Cochrane update. The remaining four trials have not been published in sufficient detail for analysis. See table 2.

Commentary

Chronic lung disease (CLD) remains a serious and common problem among very low birth weight infants despite the use of antenatal steroids and postnatal surfactant therapy to decrease the incidence and severity of respiratory distress syndrome (RDS). This condition affects nearly third of all very low birth weight infants with RDS (Henderson-Smart et al.). The aetiology of CLD is multifactorial and lung inflammation due to mechanical ventilation, oxygen toxicity, or infection contributes to its development. A well performed systematic review (Henderson-Smart et al.) did not find any substantial

Table 2 High frequency oscillatory ventilation versus conventional mechanical ventilation in very low birth weight infants

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
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<tbody>
<tr>
<td>Henderson-Smart et al (2002)</td>
<td>13 RCTs (over a period of 12 years) (1553) [comparing HFOV v CV for acute pulmonary dysfunction, mainly due to RDS in preterm infants. Randomisation and commencement of treatment was in the first 12 hours of life</td>
<td>Systematic review (level 1a)</td>
<td>CLD or mortality at 36 weeks CGA</td>
<td>Summary relative risk (RR) for death or CLD at 36 weeks CGA was 0.82 (95% CI 0.69 to 0.99) (5 trials, n=788)</td>
<td>Changing obstetric and neonatal practices may influence the genesis of CLD interventions vary according to type of ventilator used and strategy for HFOV and CV</td>
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<td>Johnson et al (2002)</td>
<td>797 infants between 23–28 weeks gestation and needing intubation since birth. Infants with major congenital malformations and those needing transfer to other hospital were excluded from the trial. Infants assigned to HFOV or CV within first 1 hour after birth. Switching of ventilation strategy was permitted after 120 hours or in first 120 hours if there was treatment failure</td>
<td>RCT (level 1b)</td>
<td>CLD or death at 36 weeks CGA</td>
<td>RR 0.98 (95% CI 0.89 to 1.08)</td>
<td>Most infants were changed to CV for weaning purposes (median 3 days, IQR 1–6 days)</td>
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<td>Courtney et al (2002)</td>
<td>498 infants between 601–1200 g, appropriate for gestational age, received one dose of surfactant, requiring CV with FiO2 of at least 0.25 and mean airway pressure of 6 cm, &lt;4 hours of age, and expected to need mechanical ventilation for more than 24 hours</td>
<td>RCT (level 1b)</td>
<td>CLD or death at 36 weeks CGA</td>
<td>RR 0.79 (95% CI 0.69 to 0.96)</td>
<td>Conservative extubation criteria for CV (FiO2 ≤0.25 and MAP ≤5)</td>
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advantage of HFOV over CV in management of preterm infants with RDS. The authors concluded that the borderline benefits of HFOV in terms of CLD appear to be outweighed by concerns about increased rates of IVH and airleaks, despite the fact that these side effects are not statistically significant. The two largest contemporary trials (Johnson et al and Courtney et al) published recently showed contrasting results. The results of the study by Johnson et al were similar to the majority of previous trials which did not show a difference between the two modes of ventilation for the combined outcome of CLD or death. In contrast, Courtney et al found a small difference favouring HFOV. These two trials were very different in their ventilatory strategy. The trial by Johnson et al provided target guidelines for blood gases and specified only the inspiratory time and ventilatory rate. The rest of the ventilatory management was at the discretion of the attending clinician and reflects common NICU practice around the world. On the other hand, the ventilatory strategy in the study by Courtney et al was strictly protocol based.

So, what do we find? Even in the most well controlled situations and experienced hands, HFOV does not confer a clinically significant advantage in terms of CLD and mortality at 36 weeks.

We extracted data from the Cochrane systematic review (Henderson-Smart et al) for the trials comparing HFOV using high volume strategy versus CV and combined that with the data from the trials by Johnson et al and Courtney et al. The resulting meta-analysis (seven trials and 2069 infants) showed a borderline statistically significant reduction in the incidence of CLD or death in the HFOV group (summary RR 0.90, 95% CI 0.83 to 0.98; NNT 20, 95% CI 11 to 100). There was no evidence of difference in the incidence of grade 3 or 4 IVH (summary RR 0.97, 95% CI 0.78 to 1.19) or pulmonary airleaks (summary RR 1.04, 95% CI 0.87 to 1.25).

Can surfactant cure babies with severe bronchiolitis?

Report by
Munib Haroon, PICU Fellow, Leeds General Infirmary, UK

You are an intensive care registrar who has taken over the care of a 3 week old baby boy diagnosed as having clinical bronchiolitis (now found to be RSV+). He was initially admitted and ventilated because of increasing respiratory distress and apnoeas. His ventilatory requirements are increasing and gas exchange is getting worse. You have just

<table>
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<th>Table 3</th>
<th>Surfactant in babies with severe bronchiolitis</th>
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<tr>
<td>Citation</td>
<td>Study group</td>
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<tr>
<td>Tibby et al (2000)</td>
<td>19 infants, 9 receiving 2 doses of surfactant with ventilation, 10 ventilation plus placebo</td>
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<td>Luchetti et al (1998)</td>
<td>20 children, 10 ventilated and given surfactant; 10 ventilated only</td>
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<tr>
<td>Vos et al (1996)</td>
<td>2 infants. Both ventilated and given surfactant</td>
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</table>

CLINICAL BOTTOM LINE
• The aetiology of chronic lung disease is multifactorial and choice of ventilation does not affect its incidence.
• High frequency oscillatory ventilation (HFOV) is probably not superior to conventional ventilation as primary mode of ventilation in preterm infants with respiratory distress syndrome for prevention of chronic lung disease or mortality at 36 weeks. However, use of HFOV is safe and not associated with increased risk of intraventricular haemorrhage or airleaks.
• Important long term neurodevelopmental outcomes should be addressed for infants treated with HFOV, as should the economic effects of introducing a new mode of ventilation.

REFERENCES
finished your stint on neonates and recall hearing that surfactant has been used on infants with bronchiolitis in trials. You wonder if it may help this child.

**Structured clinical question**

In an infant with severe RSV+ bronchiolitis requiring ventilation [patient], does endotracheal surfactant [intervention]; (a) improve ventilation/gas exchange parameters; and (b) shorten the duration of ventilation or intensive care stay [outcome]?

**Search strategy and outcome**

A search string of (a) [bronchiolitis] and [surfactant] and (b) [respiratory syncytial virus] and [bronchiolitis] was used.

Cochrane database—topic registered only.
PubMed—three relevant papers; 85 hits.
SUMSearch—nothing other than the above.
See table 3.

**Commentary**

To date no systematic review has been performed on this topic, but the number of trials published to date is very small. Thus there is limited evidence available on the therapeutic merit of surfactant in bronchiolitis.

Both trials summarised above show an improvement in ventilation and gas exchange parameters with surfactant. However other than these (surrogate) end points there is a lack of evidence to show that an infant with severe bronchiolitis will either require a shorter period of ventilation, or a reduced time in an intensive care setting.

The earlier trial (Vos et al), while showing statistically significant reductions in ventilation time and intensive care stay, had some limiting factors. Blinding was not carried out and only four cases were shown to be RSV+. Given that bronchiolitis can be due to different viruses and these all could affect children with varying severities, this is an important point to bear in mind when considering RSV+ bronchiolitis. Interestingly the average age of the cases in Vos et al’s trial was 10.4 months; this may not reflect the typical PICU bronchiolitic “intake” in many other units, bronchiolitis usually being more severe in younger babies. It is worth asking therefore how generalisable this paper’s findings are, given that they relate to infants who are not all RSV+ and who are older than those usually seen in a PICU.

The more recent trial by Tibby et al was a blinded trial, but was of insufficient power to show statistically significant changes in ventilation and PICU stay. There were several differences between this trial (Tibby et al) and the previous one which warrant consideration. This trial comprised younger patients (mean age <10 weeks), all of whom were RSV+ and were treated with larger doses of surfactant (100 mg/kg v 50 mg/kg). Thus as well as knowing their RSV status, we know they were more representative of a PICU population of bronchiolitics. However, with two trials both using different doses, we can ask which dose has the optimal efficacy.

No complications were reported in these studies, but it is worth reflecting on the fact that surfactant treatment does not go without its own hazards such as a small increase in the rate of pulmonary haemorrhage. Furthermore, surfactant is not cheap and there needs to be evidence showing real clinical improvements rather than improved short term physiological parameters to recommend its use. More or larger trials (including phase 2 trials or trials with multiple arms to look at surfactant doses) are needed to look at the role of surfactant in improving time based outcomes, such as ventilation duration and length of hospital/PICU stay and survival.

**REFERENCES**