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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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 focussing 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 Sackett1 and Moyer2 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:

• Are topical corticosteroids superior to systemic histamine antagonists in treatment of allergic seasonal rhinitis?
• Do behavioural treatments for sleep disorders in children with Down’s syndrome work?
• Inhaled steroids in the treatment of mild to moderate persistent asthma in children: once or twice daily administration?

N of 1 trials

Some therapies seem to have a general effect on most patients with a condition—paracetamol for fevers, as an example. Other drugs certainly improve the life of some children, but have no effect on others (DNase in cystic fibrosis seems to be like this). These medicines, especially for chronic conditions, are often given for a limited time in order to see if they have an effect. The “N of 1” trial seeks to advance the basic idea of a “therapeutic trial”, by putting it onto a more scientific footing.

The format is to randomise between receiving active therapy and placebo, then receive the other. This should be repeated. Practically, this needs consent and understanding of the parents and child, appropriate and agreed outcome measures, and a friendly pharmacy to make up the medicines for you.

These trials have been used in many areas in adult medicine, and have been reported in paediatrics.1 2 They are difficult to perform, needing to acquire placebos, capture outcomes accurately, and have a degree of statistical analysis. They have a great strength: they may prevent a child taking a treatment which is doing no good, or allow a child to gain benefit from a drug which has great interpersonal variation.


REFERENCES

4 http://cebm.jr2.ox.ac.uk/docs/levels.htm [accessed July 2002).

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Additional information on each of the topics is available on the ADC website (www.archdischild.com)
Are topical corticosteroids superior to systemic histamine antagonists in treatment of allergic seasonal rhinitis?

Report by
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Johannes Forster, Professor of Paediatrics, St Josef Krankenhaus Padiatrie (St Hedwig), Freiburg, Germany

You receive a call from one of your adolescent patients, a 16 year old boy with a longstanding history of seasonal allergic rhinitis (SAR). He is currently treating his mainly nasal symptoms with an oral histamine antagonist (OH1A). His symptoms are getting increasingly difficult to control. He is worried about the upcoming hay fever season and asks for other treatment options.

Structured clinical question
In a 16 year old [patient] are topical corticosteroids [intervention] more effective than oral histamine antagonists [comparison intervention] in the alleviation of symptoms of seasonal allergic rhinitis [outcome]?

Search strategy and outcome
Search engine—PubMed: “allergic rhinitis and adrenal-cortex-hormones and meta-analysis” (MeSH-Terms).
Search results—two articles found, one original meta-analysis.
Secondary sources—Consensus Statement, European Academy of Allergology and Clinical Immunology.

See table 1.

Commentary
The meta-analysis by Weiner et al was easily identified using the search terms from the structured clinical question. Once the internet database PubMed was accessed the paper could be reviewed online through the BMJ website (http://bmj.com). The secondary source of van Cauwenberge et al was suggested by a medical colleague and was likewise viewed on the internet through its publisher’s website (http://www.blackwell-synergy.com). Both papers were readily available, but of very different quality and use to our clinical scenario. The meta-analysis by Weiner et al gives detailed information about the process of identification and review of the primary data. In particular, it is structured along the rigorous methodology of a Cochrane review. The findings are presented in easily comprehensible tables and the limitations of the individual results are discussed in satisfactory detail. The consensus statement by van Cauwenberge et al is a concise document dealing with all issues and treatment options related to SAR. However, the authors give no details on the identification and review process of the evaluated literature. The paper therefore ranks lowest (level 5) in the hierarchy of evidence for clinical decision making. Its clinical bottom line is partially based on the study by Weiner et al, the result of the primary literature search.

With regard to the effectiveness and safety of OH1A and intranasal corticosteroids (INC), both come in once daily to twice daily applications, depending on the preparation used. First generation antihistamines have significant sedative and anticholinergic side effects. Such side effects are less pronounced in second generation antihistamines. In patients with liver disease or concomitant treatment with drugs metabolised through the cytochrome P450 system (antifungal agents or macrolide antibiotics) significantly increased drug concentrations are associated with serious side effects. In particular, terfenadine and astemizole have been associated with

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Topical corticosteroids v systemic histamine antagonists in treatment of allergic seasonal rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citation</strong></td>
<td>Weiner et al (1998)</td>
</tr>
<tr>
<td><strong>Study type and type of evidence</strong></td>
<td>Systematic review, level of evidence 1b (SR with predominantly homogenous RCT)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Meta-analysis of 16 RCT (total of 2267 subjects, mean age 23 years, range 12 to 75 years)</td>
</tr>
<tr>
<td><strong>Comparison INC v OH1A on nasal symptoms</strong></td>
<td>Combined standardised mean difference (SMD) −0.32 (95% CI −0.53 to −0.12). Level of evidence 1a (SR with homogeneity of RCT)</td>
</tr>
<tr>
<td><strong>Comparison INC v OH1A on eye symptoms</strong></td>
<td>No significant difference between INC and OH1A. Meta-analysis of 11 RCT. OH1A could be beneficial ancillary to INC for treatment of eye symptoms.</td>
</tr>
<tr>
<td><strong>Total outcome</strong></td>
<td>INC are recommended as first line treatment of allergic rhinitis. No comment on identification of primary data or appraisal of the underlying evidence. Safety issues were considered. Recommendation partially based on van Cauwenberge et al (2000) Consensus statement. Advice on treatment of seasonal allergic rhinitis. Level 5: expert opinion without explicit critical appraisal.</td>
</tr>
<tr>
<td><strong>INC</strong></td>
<td>Intranasal corticosteroids; OH1A, oral H1 receptor antagonists.</td>
</tr>
</tbody>
</table>
fatal cardiac side effects. Never antihistamines (cetirizine (Zirtek), fexofenadine (Telfast), and loratadine (Claritin)) are not metabolised via the cytochrome P450 system and are considered safe if drug specific recommendations are followed. Topical corticosteroids are known to occasionally cause predominantly mild local side effects (crusting, dryness, epistaxis). The topical application of low drug doses and low drug availability avoids high systemic drug concentrations and potential hypothalamic pituitary adrenal axis suppression, a serious complication of systemic corticosteroid treatment. No systemic side effects are recognised for fluticasone propionate and budesonide; systemic side effects have been described for dexamethasone spray and betamethasone drops only. However, caution is warranted in patients with a co-morbidity of asthma when inhaled corticosteroids are used alongside nasal corticosteroid preparations to avoid cumulative doses.

A variety of INC preparations are available. Costs vary from £5.85 (budesonide aequos spray, Rhinocort Aqua) to £11.43 (fluticasone propionate, Flonase) in the UK. Few comparative studies are available on the effectiveness of different steroid preparations. Most of these studies are limited to perennial SAR. All INC are effective in alleviating nasal symptoms but aqueous preparations seem to be favoured by the majority of patients. Most studies describe treatment with budesonide 256 µg once daily to be more effective than the comparison INC. Budesonide has a good safety profile and is cost effective.

REFERENCES

Do behavioural treatments for sleep disorders in children with Down’s syndrome work?

Report by
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Kristin Liabo, Research Officer, City University
Helen Roberts, Professor of Child Health, City University

A mother brings her 7 year old son with Down's syndrome to clinic complaining of sleep difficulties. He won’t go to sleep alone, frequently wakes in the night, and will not be settled unless transferred to his parents’ bed. His parents are exhausted, and his mother believes his lack of sleep is also disrupting his daytime behaviour. He has always been difficult to settle and seldom slept through the night without waking. The child is overweight, but not obese, and on enquiry his mother tells you that he does not usually snore, or suffer from nocturnal enuresis (bedwetting), which makes obstructive sleep apnoea an unlikely cause. His mother tells you, “I’m sure he’s just waking up out of stubbornness and not because anything’s wrong, but we’re all worn out. I don’t know what to do.” You wonder if a behavioural treatment programme might be able to help in this situation.

Structured clinical question
Can behavioural programmes [intervention] work to tackle sleep difficulties [outcome] for children with Down’s syndrome [patient] where there is no clear physical cause for the sleep problems?

Search strategy and outcome
Using Cochrane library—“sleep*” and “child*” Cochrane reviews: 0 relevant; Cochrane Database of Reviews of Effectiveness: two relevant; using Medline, Psychinfo: “sleep*” AND “developmental disabilities” limit to child and review articles: one relevant. See table 2.

Commentary
Three reviews of evidence on this topic were located. Only one of these reviews searched the grey literature or included non-English language publications. The other reviews provided insufficient information on search procedure to be certain that they were systematic. Reviews of prevalence suggest that occurrence of sleep disorders among children with developmental disabilities is high.

The evidence available would suggest that behavioural interventions are successful for young children without developmental disabilities. Caution should be used when considering the potential impact of intervention on sleep problems owing to the heterogeneity of the presenting problems, the subjects used, the changes measured, and the programmes implemented. These problems may be exacerbated when using children or infants as subjects. The definition and treatment strategies for a sleep disorder in a 6 month old baby cannot be assumed to be equivalent to definition and treatment strategies in a 6 year old child. In particular, it may be inappropriate to assume that findings from samples of younger, non-disabled children are necessarily applicable in this instance.

The review of behavioural interventions for sleep difficulties with young adults and children with learning difficulties would suggest that behavioural interventions are also efficacious in this group. However, because of the shortage of studies in this area, single case studies and non-controlled studies were included in the review, and size of effect could not reliably be assessed. These factors are likely to overestimate intervention effects. Particular problems with conducting research within this area were highlighted by this review. Treatment “overlap” seemed to be common; for instance, in some studies melatonin was used in conjunction with behavioural interventions, making it difficult to attribute cause to the observed effects on sleep. (But see Archimedes from September 2002 for more on this—Ed.) Families prefer behavioural interventions in the first instance. However, the success of such interventions will also depend on the parents’ ability and motivation to implement them. Studies do not appear to have evaluated adherence to behavioural programmes, which may be problematic for interventions that advocate not responding to crying or disruptive behaviour.
There is little evidence to favour one behavioural intervention over another. Alternative strategies are:

- **Sleep scheduling/scheduled awakening.** Altering sleep pattern by instituting fixed bedtime and waking time. Sleep outside of scheduled times is avoided, although fixed naps during the daytime may also be scheduled.

- **Combination of bedtime routine and gradual distancing from parents.** Establishing positive bedtime routines. Parental involvement is gradually reduced; for example, sleeping in the same bed is gradually reduced by the parent moving from bed to sitting next to the bed until the child is asleep, then replaced with a doll.

- **Bedtime fading with or without response cost.** The retraining of bedtime habits by beginning bedtime at a relatively late time when child will fall asleep quickly, then gradually bringing bedtime forward until desired bedtime is achieved. Response cost involves the child being taken out of bed for a certain period if he or she doesn’t fall asleep within a specified time.

- **Extinction.** Bedtime fading and gradual withdrawal of parental involvement. The parents re-enter the room, encouraging the child to sleep at intervals of 3–5 minutes; these intervals are increasingly extended.

No evidence was found which would suggest a behavioural intervention would do harm. In comparison, treatment of sleep breathing disorders, in the absence of infection, involves physical intervention (invasive treatments with poor evidence for efficacy) or drug treatments, which may cause side effects. Nonetheless, the impact on the child and family of extinctions strategies should be considered.

We would like to acknowledge the contributions of Professor Tricia Sloper, at York University, for drawing our attention to this important problem, and Dr Paul Ramchandani, Oxford, for his comments.

**REFERENCES**


Inhaled steroids in the treatment of mild to moderate persistent asthma in children: once or twice daily administration?

Report by Daniele Radzik and Luigi Pavanello, Paediatric Department, San Giacomo Hospital, Castelfranco Veneto, Italy

A 6 year old girl comes to your outpatient paediatric clinic with a two month history of cough and shortness of breath, requiring, nearly three times a week, administration of β2 agonists by jet nebuliser. She has often been noticed to wheeze at school during the gymnastic class, and also when she’s laughing or crying; almost once a week she awakes during the night complaining of cough and respiratory difficulties.

Your diagnosis is persistent asthma, and after a short course of nebulised salbutamol (albuterol) and oral steroids you decide to start, twice a day, prophylaxis with inhaled steroids, via a spacer device. As her mother is working away from home until late afternoon, she asks you if a once daily administration would have the same efficacy.

Structured clinical question
In children with mild to moderate persistent asthma [patient] does once daily and twice daily administration of inhaled steroids [intervention] have the same efficacy [outcome]?

Table 3 Dosage regimen of inhaled steroids in asthma

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type (level of evidence from the Oxford CEBM)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al (1998)</td>
<td>167 children, aged 5–12 y with symptomatic asthma, multicentre study</td>
<td>Double blind RCT (level 1b) Jadad score: 2</td>
<td>PEF, FEV1, FVC, wellbeing and symptom score, albuterol use, adverse events</td>
<td>OD &gt; BID for evening PEF: ±19.7 l/min v ±8.3 l/min (p&lt;0.013); no other significant differences (morning PEF: +24.6 l/min v +13.2 l/min, p=0.059)</td>
<td>Ten patients excluded from the all-patients treated population; a greater number of patients randomised to the BID arm: 90 v 77 Patient compliance not assessed</td>
</tr>
<tr>
<td>Jonasson et al (1998)</td>
<td>163 children, aged 7–16 y, with mild asthma, outpatient clinic</td>
<td>Double blind RCT (level 1b) Jadad score: 3</td>
<td>PEF, FEV1, FVC, symptom score, β2 agonist use, exacerbation, exercise test, adverse events</td>
<td>OD in BID budesonide: Absolute reduction in FEV1% −0.05 (95% CI −3.3 to +3.0); Absolute reduction in PEF 2.9 l/min (95% CI −10.8 to +16.6)</td>
<td>Patients with near normal lung function: FEV1 at baseline &gt;100%, reversibility of 95%</td>
</tr>
<tr>
<td>Heuck et al (1998)</td>
<td>24 children, aged 5–12.5 y, with mild asthma, outpatient clinic</td>
<td>Double blind RCT (level 1b) Jadad score: 3</td>
<td>Lower leg growth, PEF, symptom score, albuterol use, markers of collagen turnover</td>
<td>Significant reduction of lower leg growth rate (p&lt;0.04) and markers of collagen turnover with BID OD v BID budesonide: Absolute reduction in morning PEF (95% CI −4.2 to +15 l/min), in evening PEF (95% CI −3.8 to +16 l/min)</td>
<td>Small study, the trial did not include a placebo period</td>
</tr>
<tr>
<td>Moller et al (1999)</td>
<td>206 children, aged 5–15 y, with stable asthma, multicentre study</td>
<td>Double blind RCT (level 1b) Jadad score: 3</td>
<td>FEV1, FVC, FEV1% PEF, symptom score, albuterol use, adverse events</td>
<td>OD in BID budesonide: Absolute reduction in morning PEF −2.8 l/min (95% CI −10.4 to +4.5); Absolute reduction for FEV1% −0.08 (95% CI −3.4 to +0.9)</td>
<td>Difference in patients demographic characteristics (duration of asthma in months) between OD and BID</td>
</tr>
<tr>
<td>Baker et al (1999)</td>
<td>480 children, aged 6 mth to 8 y, with moderate persistent asthma, multicentre study</td>
<td>Double blind RCT (level 1b) Jadad score: 2</td>
<td>FEV1, PEF, symptom score, adverse events and in a subgroup trialal testing</td>
<td>0.50 mg BID budesonide v placebo: absolute reduction for FEV1 in l/min 0.13 (p&lt;0.05); 1 mg OD budesonide v placebo: absolute reduction for FEV1 in l/min 0.07 (NS)</td>
<td>Lost to follow up: 27% Differences in % patients using inhaled steroids before entering into the study between OD and BID groups</td>
</tr>
<tr>
<td>Jonasson et al (2000)</td>
<td>122 children, aged 7–16 y, with mild asthma, outpatient clinic</td>
<td>Double blind RCT (level 1b) Jadad score: 3</td>
<td>FEV1, FEF25–75, PEF, exercise test, metacoline challenge, symptom score, growth rate, ascorphinol count, compliance</td>
<td>No significant differences between BID and OD</td>
<td>Compliance declined rapidly</td>
</tr>
<tr>
<td>LaForce et al (2000)</td>
<td>242 children, aged 4–11 y, with persistent stable asthma, multicentre study</td>
<td>Double blind RCT (level 1b) Jadad score: 3</td>
<td>FEV1, PEF symptom score, nighttime awakening, albuterol use, adverse events</td>
<td>BID v OD fluticasone: Absolute reduction for FEV1 change in % (95% CI −11.28 to −0.124); for morning PEF (95% CI −27.26 to +9.26)</td>
<td>Asthma had to remain stable for all the study period, high rate of discontinuation in the placebo group</td>
</tr>
</tbody>
</table>

Search strategy and outcome
The search was conducted independently by two reviewers (the authors).

Medline 1966 to December 2001 using OVID interface, Cochrane Library (2001), PubMed clinical queries using “inhaled steroids” OR “glucocorticoids” OR “glucocorticosteroids” OR “budesonide” OR “mometasone” OR “flunisolide” OR “fluticasone propionate” OR “beclomethasone dipropionate” AND (“once versus twice” OR “once with twice daily” OR “OD” OR “BID administration”) AND “asthma”. Limits: all children: 0–18 years, randomised controlled trial.

Clinical evidence—no systematic reviews; 29 studies found, seven were relevant. (Papers available as abstracts only and studies including both adults and children aged >12 were excluded.) See table 3.

Commentary
As the study of Baker et al evaluated the efficacy of different doses of budesonide (four groups) compared to placebo, six studies were found that specifically compare the once daily versus twice daily administration of inhaled steroids.

Overall the methodological quality of the included studies was not always satisfactory; although most of the references mentioned the number of patients excluded from the study, withdrawals and drop outs were described and commented on only in the papers by Heuck et al and Moller et al; intention to treat analysis was reported to be used by Jonasson et al and by LaForce et al; allocation concealment was unclear in most of cases and often details of methods used to generate the random allocation sequence were lacking.
This overview found a heterogeneous group of trials with different results; although the majority of studies reported no significant difference between the two regimens, the overall findings of the seven studies are not sufficient to support the evidence that administering inhaled steroids once daily and twice daily has the same efficacy.

REFERENCES

POSTCARD FROM DOWN UNDER

Nuclear family

I t is the concept of every generation that their own childhood took place during the end of an era. I’m guessing that this more accurately reflects the rose-tinted spectacles view of our childhood that many of us have. In truth there are so many changes happening all the time—the motor car, world wars, television, computers, the internet, sliced bread—that it is easy for our internal pundit to draw the conclusion that, say, the invention of the toaster really did signify the end of one era and the start of another. I need then to be especially careful when I propose that Things Have Changed with respect to the family. I think I have a basis though.

When I was aged ten and in junior school I was fairly sure—in the way that small boys can be sure about these things—that I was the only one in my class with divorced parents. This is not to imply a school in a particularly affluent or advantaged area, but instead an average school with ordinary children, and, I thought, ordinary parents. Aged 14 in senior school my individual status had altered, although those of us from “broken homes” were still in a minority. The phrase puzzled me though, even then. I could see what was broken about my family, but not about my homes (now plural) where I was loved and nourished and supported. The dangerous idea crept into my mind that maybe I was from a more advanced place than those folk I knew whose families weren’t yet overly broken, but their homes probably were; their homes did not support them in the way mine did.

Later, 20 years old and at university, I met someone who told me that she’d never known anyone at her school with divorced parents. By this point, even my minority status was under threat, and I found her statement so unusual that I felt it said more about her background than mine. These days I’m surprised when taking a history if the family tree is a straightforward nuclear family. I find myself with very mixed feelings if I pause to examine this surprise. More and more the concept of “normality” is tested. Should the word mean the same as average, or more accurately median? Or should it mean, in this context, acceptable? How about desirable? When I say that I would prefer children to be brought up in a normal environment, what am I actually asking for and, additionally, what am I implying about what I regard as my own excellent— but, by many definitions abnormal— upbringing?

More and more our concept of “normality” is tested.

Australian law has recently increased the legal strength implicit in a de facto or common law relationship. For example, my wife and I confer upon each other, by legal strength of our marriage, the same rights on each other as a couple who have been in a de facto relationship for, depending on the circumstances, six months to two years. Put another way, after two years it is as if you are married. Yet another way: you might as well be married. Some might say that this just another piece of evidence pointing to the progressive trivialisation of marriage as an institution. Others might point out that, for many, the institution has been brought so low that it represents merely a brief prolongation of a one night stand, so it can hardly be made more trivial.

The truth, as it usually is, is probably something more complex. What has been getting clearer to me ever since the seed was sown by folk talking their “broken home” nonsense is that family is a much more fluid and difficult concept than I’ll ever fully grasp. At the same time that there are wonderful conventional families out there, (Shirley Temple orphan’s dream families where everyone is happy, even the dog) there are also some wonderful unconventional families too. We can all bring to mind the apparently broken family which we loaded with burdens—usually medical—in the certain knowledge that they would not cope, “not under their circumstances”. But cope they did, probably better than we would have.

The converse is that some families fail, and fail badly. And we all know other families which are apparently “nuclear”, but on closer examination are so toxic that they only really earn the nuclear description by comparison with the spent fuel rods from a nuclear power plant.

I’m sure that most of us have been intuitively shifting our concept of family for years. I’m not courageous or clever enough to suggest how we should define what a family really is. I would say, however that it is far too important an issue (and too much of the end of an era) to leave to politicians, the media, or even religious leaders the task of defining what a “proper, normal” family should be.

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Are topical corticosteroids superior to systemic histamine antagonists in treatment of allergic seasonal rhinitis?

Charles C Roehr and Johannes Forster

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