ARCHIMEDES

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. 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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,[2] and gaining answers.[3]) 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.[4] 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[5] and Moyer[6] 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.

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.

- Does early administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?
- Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia?
- Do steroids help children with acute urticaria?

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Rule 31: Review the world literature fortnightly

In his book *Kill as few patients as possible*[1] Oscar London suggests we review the world literature fortnightly. At an estimate rate of 10 RCTs added to Medline *per day*, there's little chance of this happening.

Instead, it's been widely suggested that doctors focus their reading on clinical questions which are relevant to their practice. But thousands of questions assault us at every turn, professionally and privately. They range from the ordinary (''What should I have for lunch?'') to the exceptional (''I wonder if β interferon will reduce relapses in this 7 year old with an aggressive demyelinating condition?'').

Questions can be divided into those which seek general, broad information and those which address a particular problem. (The former—background questions—are actually a combination of lots and lots of specific questions, but addressing each step is unfeasible.) The latter are known as ''foreground questions'' or ''specific questions''.

One way of focusing the deluge of questions is by recording clinical questions as they arise, in the structured format[2] we use in Archimedes.

We ask too many questions to answer them all in this way, so be sensible.[3] Here are a few hints to make evidence based practice possible:

- Use the evidence based process to answer questions which crop up time and time again; you're more likely to find someone will have studied them, and you are more likely to be able to implement the answer you develop. Ignore questions which have limited applicability.
- Work with colleagues to answer each other's problems, perhaps by restructuring your journal club.[4] In this way you can work with the individual strengths and all improve on your weaknesses.
- Consider using the range of ''pre-appraised'' resources (like Archimedes, BestBets, and Clinical Evidence) to get to the answers quickly.
- Give yourself a time limit—and if you haven't found an answer, work with the best information you can.

Finally, if in your work your think your have a really interesting question and answer which other people should be able to read, submit it as an Archimedes topic (see www.archdischild.com for details).

References

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Additional information on each of the topics is available on the *ADC* website (www.archdischild.com/supplemental)

Does early administration of dexamethasone improve neurological outcome in children with meningococcal meningitis?

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A 6 month old boy was admitted to the paediatric ward with history of fever, non-blanching petechial rash, shrill cry, and poor capillary refill. He required 20 ml/kg of fluid bolus. After a full sepsis screening including a lumbar puncture, he was started on intravenous cefotaxime for a presumed diagnosis of meningococcal meningitis. Next day on the ward round the specialist registrar wondered if a short course of dexamethasone should have been started with the first dose of antibiotic to improve neurological outcome in this child.

Structured clinical question

In children with meningococcal meningitis [patient group] does early treatment with dexamethasone [intervention] reduce the frequency of sensorineural hearing loss or other neurologic sequelae [outcome]?

Search strategy and outcome

Cochrane Database and Medline using PubMed interface.

Search words: ''meningitis'' AND ''steroids''; ''meningococcal'' AND ''steroids''; ''meningitis'' AND ''dexamethasone''.

Limits (in PubMed): study type: randomised control trial; language: English.

Search outcome: 32 hits; four directly relevant to the question; one metaanalysis. See table 1.

Commentary

There appears to be a paucity of studies on the effects of adjunctive therapy with steroids in children specifically with meningococcal meningitis. Earlier studies[4 5] done in children with bacterial meningitis, suggest improved neurological outcome with dexamethasone. However, the majority of children in these studies had *H influenzae* meningitis and hence these could not be considered as being representative studies for meningococcal meningitis. These results were reflected in a meta-analysis of randomised control trials assessing improved neurological outcome with dexamethasone in bacterial meningitis.[1] The later study on adults by Thomas and colleagues,[2] which had a mix of patients with pneumococcal and meningococcal meningitis, was inconclusive regarding systematic use of dexamethasone as an adjunctive therapy for bacterial meningitis. Meningococcal meningitis appears to have the lowest risk of major neurological sequelae compared with pneumococcal and *H influenzae* meningitis.[1 6] In a multicentre prospective study on 124 children with bacterial meningitis by Richardson and colleagues,[7] the children treated with steroids actually had a higher incidence of hearing loss (relative risk 1.70). In this population of children, hearing loss was more common in children who had been ill for more than 24 hours (relative risk 2.72; 95% CI 0.93 to 7.98) and hence the authors hypothesise that there is a critical period around second day of illness, during which hearing loss can be reversed, provided appropriate antimicrobial and supportive treatment is commenced.

Pollard and colleagues[8] recommend a two day course of dexamethasone as an adjunctive treatment for children with bacterial meningitis, but admit that no data were available for meningococcal meningitis. None of the studies have stratified their results according to serotype of the causative organism or age group of patients, but the subjects in the paediatric studies were outside the neonatal period. It appears, hence, from the review of current best evidence, that use of dexamethasone as an adjunctive therapy could improve neurological outcome in children with suspected *H influenzae* meningitis and possibly pneumococcal meningitis. However, its use cannot be routinely recommended in cases of suspected meningococcal meningitis or in any case where the aetiology is uncertain.[9]

CLINICAL BOTTOM LINE

- Currently there is not sufficient published evidence to recommend early use of dexamethasone in order to improve neurological outcome in children with meningococcal meningitis. In fact, there is some evidence that its use in such a situation might be disadvantageous as far as hearing is concerned.

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Table 1 Dexamethasone in meningococcal meningitis

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
McIntyre *et al* (1997)	848 children with bacterial meningitis with mean age in studies 1.2 to 7 y	Meta-analysis of 11 randomised controlled trials. Non-randomised studies assessed for adverse effects (1a)	Hearing loss and neurological outcome other than hearing loss	In *H influenzae* meningitis dexamethasone reduced severe hearing loss (OR 0.31, 95% CI 0.14 to 0.69). Pneumococcal meningitis OR 0.52 (95% CI 0.17 to 1.46). Protection against other neurological deficits was not statistically significant (OR 0.59, 95% CI 0.34 to 1.02)	Authors do not report a method for assessing validity. Difference between subgroups may be observed by chance. Potential publication bias
Thomas *et al* (1999)	60 adult patients with bacterial meningitis	Multicentre, double blind, randomised trial (1b)	Rate of patients cured without clinical neurologic sequelae at 30 days	Rate of cured patients without neurological sequelae was not significant (p = 0.071) between the 2 groups. RRR of severe neurologic sequelae following dexamethasone therapy was 44% (95% CI −57 to 100)	Adult patient groups. First dose of dexamethasone was given within 3 h of first antibiotic dose rather than with or before the dose
Syrogiannopoulos *et al* (1994)	118 children aged 2.5 mth to 15 y with suspected or proven bacterial meningitis	Single blind randomised control trial (1b)	Neurological and audiological assessment at 6 weeks and 4–24 months	No difference in the rate of neurologic and/or audiologic sequelae between 2 groups; RRR −135% (95% CI −11 to 100)	Both groups received dexamethasone
Schaad *et al* (1993)	115 children (age 3 mth to 16 y) with suspected or confirmed bacterial meningitis	Double blind randomised control trial (1b)	Neurologic and audiologic test at 3, 9, and 15 months	16% of 55 placebo recipients and 5% of 60 dexamethasone recipients had 1 or more neurologic/audiologic sequelae (p = 0.066); the relative risk of sequelae was 3.27 (95% CI 0.93 to 11.47)	55% of children in control group and 62% in experimental group had *H influenzae* meningitis
Odio *et al* (1991)	101 children aged 6 weeks to 13 years with suspected or proven bacterial meningitis	Double blind randomised controlled trial (1b)	Neurological follow up up to 12 months, audiologic follow up up to 24 months	Favourable neurological outcome in dexamethasone treated group; RRR 68% (95% CI 11 to 100) with NNT 6. No difference in audiologic sequelae between two groups; RRR 63% (95% CI −13 to 100)	Only 2 patients (4%) in dexamethasone group and none in control group had meningococcal meningitis

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Should nifedipine be used to counter low blood sugar levels in children with persistent hyperinsulinaemic hypoglycaemia?

Report by
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A 5 year old boy, suffering from hyperinsulinaemic hypoglycaemia since infancy and arterial hypertension secondary to polycystic kidney disease, was given nifedipine (0.3 mg/kg three times a day) to treat his high blood pressure. Normotension was restored and his blood sugar levels normalised. We wondered whether nifedipine could be used safely as long term treatment to counter hypoglycaemia in persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI)?

Structured clinical question

In a child with persistent hyperinsulinaemic hypoglycaemia of infancy [patient], can nifedipine [intervention] safely be given to treat hypoglycaemia [outcome]?

Table 2 Nifedipine in persistent hyperinsulinaemic hypoglycaemia

Citation	Study group	Study type (level of evidence from the Oxford CEBM)	Outcome	Key results	Comments
Bas *et al* (1999)	3 infants. Intervention: nifedipine 0.7, 0.5, and 0.8 mg/kg/day	Case series (level 4)	Glycaemic control	Normoglycemia on therapy, hypoglycaemia after tapering of nifedipine	Challenge–dechallenge–rechallenge studies. Follow up 12 months, side effects not reported (see ref 7)
Lindley *et al* (1996)	1 preterm baby. Intervention: nifedipine 0.7 mg/kg/day	Case report (level 4)	Glycaemic control	Blood sugar increased (from 3.5 to 4.8 mmol/l), fasting tolerance from 3 to 10.5 h	Nifedipine introduced after diazoxide, glucagon, steroids, ACTH, and pancreatectomy were unsuccessful
Suprasongsin *et al* (1999)	2 infants. Intervention: nifedipine 0.5 and 0.7 mg/kg/day plus raw corn starch 8 g/kg/day	Case series (level 4)	Glycaemic control	Persistent rise in blood sugar from baseline 1.5 mmol/l and 1.9 mmol/l	Follow up of 8 years and 14 months, side effects not reported
Eichmann *et al* (1999)	2 infants. Intervention: diazoxide and nifedipine 0.7 mg/kg/day and nifedipine 2 mg/kg/day	Case series (level 4)	Glycaemic control	One patient stable on nifedipine monotherapy, the other stable while diazoxide could be reduced	Very low baseline blood sugar levels: 0.78 mmol/l and 0.96 mmol/l, no side effects to nifedipine reported
Shanbag *et al* (2002)	1 infant. Intervention: nifedipine 0.5 mg/kg/day	Case report (level 4)	Glycaemic control	Blood sugar stable on nifedipine monotherapy	Follow up 9 months, no side effects reported
Darendeliler *et al* (2002)	4 children. Intervention: nifedipine at a median of 0.65 mg/kg/day	Case series (level 4)	Glycaemic control	All stable on nifedipine monotherapy	Follow up 4 mth to 7.3 years). 3 children from previous report[3] included.

Search strategy and outcome

Search terms: ''persistent hyperinsulinemic hypoglycaemia of infancy'' and ''hyperinsulinism'' and ''nifedipine'' and ''safety'' and ''calcium antagonist''.

Cochrane Library (nifedipine or persistent hyperinsulinemic hypoglycaemia of infancy): no relevant study found. PubMed (limits: language English; age 0–18 years): one practice guideline,[1] six case reports or patient series of PHHI treated with nifedipine,[2–7] one report on the safety of calcium channel blockers in children.[12] See table 2.

Commentary

Persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI) is the most common cause of persistent hypoglycaemia in infancy.[1] In Central Europe it is a rare disorder, occurring sporadically (incidence approx. 1:50000), but has much higher incidences (1:2500 due to a familial form) in parts of the world with high consanguinity (for example, Arabian peninsula or Scandinavia).[8] The majority of cases present in the neonatal period with pronounced hypoglycaemia. Severe long term neurological complications due to prolonged hypoglycaemia are common, hence treatment needs to be commenced immediately.[1 9 11] Genetic abnormalities of intracellular metabolic pathways or membrane cation transport have been found in 30–50% of cases, which cause constant insulin secretion through abnormally stimulated ATP-sensitive potassium channels and voltage-gated Ca^{2+} channels of the pancreatic β cell.[1 12] Initially, high doses of glucose infusions are required to establish euglycaemia, traditionally followed by a treatment with either diazoxide or long acting somatostatin (octreotide), sometimes combined with dietary measures (high in starch, glucose, or protein).[10] Partial to complete pancreatectomy is pursued in patients refractory to medical treatment, but complicated by high incidences of secondary diabetes mellitus later in life.[11]

Aims to answer our question regarding the medical treatment of PHHI by searching the Cochrane Collaboration's internet archive of systematic reviews led to no positive result. A search of PubMed revealed no relevant controlled clinical studies. One consensus statement (evidence level 5) by Aynsley-Green and colleagues[1] discussed the treatment options for hyperinsulinism in childhood and was available in electronic form: among the standard treatments of PHHI were diazoxide, chlorothiazide, and somatostatin; Ca^{2+} channel blockers were not regarded a routine treatment due to lack of convincing studies. Since the time of publication of the consensus statement, however, several case reports and case series of nifedipine for PHHI have been published which showed encouraging results.[2 4–7] In these studies, nifedipine (either alone or in combination with other drugs or dietary measures) was introduced to avoid complications of diazoxide or somatostatin treatment (abdominal discomfort, vomiting, or anorexia).[11] No severe episodes of hypoglycaemia or side effects to nifedipine (hypotension, nausea, dizziness) were reported; the longest period of follow up was eight years.[4 7] The author of the largest case series[7] was contacted and asked about his experience with nifedipine beyond the published cases. No complications in maintaining treatment were reported. A comprehensive review on the use of Ca^{2+} channel blockers in children convincingly illustrated the safety of nifedipine as long term treatment in childhood.[12]

Nifedipine has been successfully used to treat PHHI and increasing evidence from case reports suggests that it can safely be given as long term treatment without serious adverse effects. Facing the varied clinical severity of PHHI, it promises to become a valuable treatment option for some children. The mounting evidence from the quoted case reports suggests that nifedipine could be tried in patients failing the standard treatment before pancreatectomy is considered. A large, multicentre, randomised clinical trial

CLINICAL BOTTOM LINE

- Nifedipine has apparently been used successfully to treat persistent hyperinsulinaemic hypoglycaemia in infancy.
- Without further study, the value of nifedipine in the treatment cascade for persistent hyperinsulinaemic hypoglycaemia of infancy is unclear.

would be desirable to elucidate the effectiveness and safety of nifedipine in this setting.

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Do steroids help children with acute urticaria?

Report by
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A 4 year old girl presents with an itchy urticarial rash. There were no other symptoms. Her general practitioner has prescribed an oral antihistamine but the rash has persisted. You wonder if there is a role for oral steroids in this otherwise well child.

Structured clinical question

In a child with acute urticaria [patient], does the addition of oral steroids to antihistamines [intervention] lead to more rapid resolution of symptoms [outcome]?

Search strategy and outcome

Cochrane Database of Systematic Reviews using search term ''urticaria'': no relevant results.

Medline 1966 to October 2002 using the OVID interface. (''exp urticaria OR urticaria$.mp'' AND ''exp steroids OR steroid$.mp OR exp adrenal cortex hormones OR corticosteroid$.mp'') LIMIT to [human AND RCT]. Search results – 21 articles, of which two were relevant.

A further search of Medline without the RCT filter and of SUMsearch using search terms ''steroids'' and ''urticaria'' yielded no further relevant results.

See table 3.

Commentary

There are no studies specifically aimed at children with acute urticaria. These limited trials show improvement in symptoms when prednisolone is prescribed, but larger studies are needed. The decision to treat with steroids should be based

Table 3 Steroids in children with acute urticaria

Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Pollack *et al* (1995)	43 adult outpatients with acute urticaria given i.m. diphenhydramine then randomised to oral hydroxyzine plus either 20 mg prednisone 12 hourly for 4 days or placebo	RCT (level 1b)	10 point visual analogue itch score at 48 hours. Itch score at 5 days. Description of rash at 48 hours and 5 days	Mean 48 hour itch score 1.3 in prednisone group *v* 4.4 in control group. 5 day itch score 0 in prednisone group *v* 1.6 in control group. No difference between groups at 48 hours. Rash resolved completely at 5 days in prednisone group	Adult patients only. Small study, no power calculation. Rash not described at 5 days in control group
Zuberbier *et al* (1996)	109 adult and paediatric patients with acute urticaria treated with loratidine 10 mg daily or prednisolone 50 mg daily for 3 days followed by loratidine 10 mg daily until remission of symptoms	Non-randomised prospective cohort study (level 2b)	Days until cessation of whealing	65.9% of had cessation of whealing by 3 days and a further 15.9% by 7 days in loratidine group, compared with 93.8% by 3 days and a further 3.1% by 7 days in the prednisolone group. Resolution in all patients after >21 days. NNT with prednisolone for resolution of symptoms by 3 days = 4	Number of children unstated. Different exclusion criteria between groups (potentially pregnant women)

CLINICAL BOTTOM LINE

- Oral prednisolone added to antihistamines may result in decreased itch and more rapid rash resolution in acute urticaria.

on the potential benefit of decreasing symptom duration in this often self limiting illness, weighed against the potential adverse effects of therapy. However, no side effects were observed in either study.

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