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, 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 They make no attempt to statistically aggregate the data, nor search the grey, unpublished literature.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. 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—which 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.

Electronic-only topics that have been published on the BestBets site (www.bestbets.org) and may be of interest to paediatricians include:

- Does intranasal or oral sumatriptan effectively relieve migraine headaches in adolescents?
- Do we need to give steroids in children with Bell’s palsy?
- In the paediatric population, should minor mucosal tongue lacerations be sutured?
- Topical anaesthetic or lidocaine infiltration to allow closure of skin wounds in children?
- How useful is ultrasound in the diagnosis of testicular torsion?

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.

- Is polyethylene glycol safe and effective for chronic constipation in children?
- Are antiemetics helpful in young children suffering from acute viral gastroenteritis?
- Should aciclovir be prescribed for immunocompetent children presenting with chicken pox?

Rule of three

There are many “rules of three” in medicine, but one in particular stands out in the practice of critical appraisal and evidence based medicine. It’s the rule first described by Handley and Lippmann-Hand in 1983, and applies to situations where a study has found no events, or alternatively, everyone has had an event (that is, 0% and 100% outcomes). This rule of three describes the 95% confidence interval for such a situation. It is calculated by 3/n, where n is the number of subjects studied. (For accuracy, n should be greater than 30.) For example, if you have a trial where 120 children received a new antiemetic, and there were no obvious adverse events, the upper bound of the 95% confidence interval would be 3/120 = 2.5%. You could be fairly sure that no more than about 1 in 40 children would suffer a side effect from this study’s results.

It also works for the other end of the spectrum, where a new therapy (for instance a new antibiotic) has no therapeutic failures in treating impetigo in a trial of 90 children. If 45 received the new antibiotic, then the confidence interval calculated by our rule would be 3/45 = 6.6%; that is, the 95% confidence intervals would be between 93.4% and 100%.

Taking this simple rule to the reading of spectacular results gives the clinician a relatively powerful way of defining what we know instinctively to be true—no news doesn’t necessarily mean good news.

Reference


REFERENCES

4 http://catm.r2.ox.ac.uk/docs/levels.htm (accessed July 2002).
Is polyethylene glycol safe and effective for chronic constipation in children?

Report by
R Arora, R Srinivasan, Llandough Hospital, Cardiff, UK; reemaraman@doctors.org.uk
doi: 10.1136/adc.2005.072918

Chronic constipation is a frequently encountered problem in the paediatric wards and clinics. Your usual line of management has been to prescribe adequate doses of regular lactulose and use sodium picosulphate as a second line laxative or as add on treatment. Recently, you have become aware of a new drug—polyethylene glycol (PEG). As you have not prescribed this drug earlier, you want to appraise the evidence before using it in your clinical practice.

Structured clinical question
In children with chronic constipation [patients] is polyethylene glycol [intervention] better in improving stool frequency and consistency [outcome] while causing fewer side effects?

Search strategy and outcome
Primary sources
Medline via Pubmed: Search was done using headings “Child”[MeSH] AND “Polyethylene Glycols”[MeSH] AND (“Constipation”[MeSH] OR “Fecal Impaction”[MeSH]). Twenty articles were found of which eight were relevant.

To find articles that had been published but were still waiting to be indexed, another search was carried out with the terms “polyethylene glycol AND constipation AND child”’. Two further relevant articles were found.

Proceedings of major meetings: The abstract of one relevant unpublished article was also included which was presented at the 2nd World Congress of Pediatric Gastroenterology, Hepatology and Nutrition in Paris in 2004 after contacting the author and obtaining additional information.

Secondary sources
Cochrane database, BestBets: No papers found.

Summary
See table 1.

Commentary
Chronic constipation in children is a common gastrointestinal disorder encountered in general paediatric clinics and forms a substantial part of the paediatric gastroenterologist’s workload. The majority of constipated children have functional constipation and despite laxative use, success is modest. Management options include a combination of healthy eating aimed at increasing fibre and fluid intake, regular toileting, reinforcement with appropriate rewards, and laxative therapy. Combining laxative use with behavioural therapy has been shown to be better than laxative use alone. A high level of motivation and perseverance are necessary for these measures to be successful, and hence a continued search for a better laxative in terms of efficacy, safety, and compliance continues.

High dose PEG with electrolytes has been available for intestinal lavage preceding radiological and surgical procedures in children for some time. The electrolytes are added to prevent their loss through the faeces due to the large volume of the lavage, but this gives the lavage solution an unpleasant salty taste. A low dose version, such as PEG 3350, is available with electrolytes (in the UK and Netherlands) or without electrolytes (in the USA); it has been in commercial use only in the last few years and is used in much smaller volumes. It has been classed as an iso-osmotic laxative and acts by opposing absorption of water from faecal material in the large bowel and thus retaining water in the faeces, which is different from the laxatives such as lactulose which draw fluid from the body into the bowel lumen due to its high osmotic load. PEG is physiologically inert and is not absorbed or metabolised in the gut, giving it an unlimited “ceiling of action”.

From the available evidence it is clear that PEG is effective for both disimpaction and maintenance in children of all age groups with chronic constipation. The compliance with PEG treatment is high. In the controlled studies, PEG has been shown to be more effective than a placebo and lactulose, and at least as effective as milk of magnesia, with a much higher compliance than any of the others. It seems safe with or without added electrolytes. Only one of the above studies actually assessed the serum electrolyte levels post-treatment; abnormal levels were not found. Literature search did not reveal any case reports of adverse effects to the use of low dose PEG 3350 with or without electrolytes.

There are still some unresolved questions such as the issue of adding electrolytes, the most effective molecular weight of PEG (PEG 3350 vs PEG 4000), and the safety profile of the drug in all age groups. The drug appears promising, and though its use at present is mainly in those with inadequate response to other laxatives, it is increasingly being used as first line treatment.

CLINICAL BOTTOM LINE

- Low dose PEG is effective, both in the short and long term management of constipation in children.
- Low dose PEG with or without added electrolytes is safe in the treatment of constipation in children.
- More studies are needed to determine the most safe and effective form of PEG in children.

REFERENCES
### Table 1: Polyethylene glycol in constipation

<table>
<thead>
<tr>
<th>Citation, country</th>
<th>Study group</th>
<th>Study type (level of evidence)</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
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<tr>
<td>Voskuil et al (2004), Netherlands</td>
<td>100 children (6 months–15 years) with constipation received PEG 3350 or lactulose for 8 weeks. They were then asked to continue in an open-label assessment for an additional 18 weeks. 91 completed the study</td>
<td>Multicentre, double blind RCT (level 1b)</td>
<td>Clinical efficacy at 8 weeks</td>
<td>Significant increase in the mean defecation frequency/week and a significant decrease in the mean encopresis frequency/week were found in both groups. 56% (95% CI 39–70) in PEG group were successfully treated compared to 29% (95% CI 16–44) in lactulose group</td>
<td>Used PEG 3350 (with electrolytes) in lower doses than used in other studies</td>
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<td>Thomson (2004), UK</td>
<td>51 children aged 2–11 years (mean 5 y) entered a double blind treatment phase and were randomised to receive either PEG 3350 or matching placebo for first 2 weeks. After a 2 week washout period cross-over to receive alternative treatment was done for another 2 weeks</td>
<td>Double blind RCT with crossover (level 1b)</td>
<td>Stool frequency</td>
<td>Mean 3.59/week in PEG group vs 1.58/week in placebo group (p&lt;0.001) after first 2 weeks</td>
<td>Used PEG with electrolytes. Adequate wash-out before crossover. Presented at WCPGHAN 2004. Unpublished as yet.</td>
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<td>Gremse et al (2002), USA</td>
<td>37 patients aged 2 to 16 years with constipation received either PEG 3350 or lactulose for 2 weeks followed by the other agent for 2 weeks as part of an unblinded, randomised, crossover design</td>
<td>RCT with crossover (level 1b)</td>
<td>Stool frequency</td>
<td>Increased from 1.7 ± 0.8/wk to 14.8 ± 1.4/wk for PEG 3350 and 13 ± 1.5/wk for lactulose</td>
<td>No wash out period during crossover</td>
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<td>Youssef et al (2002), USA</td>
<td>4 doses of PEG 3350: 0.25 g/kg/day, 0.5 g/kg/day, 1 g/kg/day, and 1.5 g/kg/day were given for 3 days in 41 children with constipation for &gt;3 months and evidence of faecal impaction</td>
<td>Individual double blind RCT (level 1b)</td>
<td>Disimpaction</td>
<td>Disimpaction achieved in 30 children (75%). 95% of higher dose patients (1–1.5 g/kg/day) achieved disimpaction vs 55% of low dose patients (0.25–0.5 g/kg/day)</td>
<td>Demonstrated the use of PEG 3350 for disimpaction and dose response relation</td>
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<td>Loening-Baucke (2002), USA</td>
<td>28 children with constipation treated with PEG (0.5–1 g/kg/day) were compared with 21 children treated with milk of magnesia (1–2.5 ml/kg/day)</td>
<td>Individual case-control study (level 3b)</td>
<td>Efficacy</td>
<td>On 3 monthly follow ups for a year, bowel movement frequency increased and soiling frequency decreased significantly in both groups. But compared to children on milk of magnesia those on PEG were soiling more frequently (p&lt;0.01) and fewer had improved (p&lt;0.01) at the 1 month follow up. This difference disappeared at subsequent follow ups</td>
<td>Not randomised. Demonstrated a high level of compliance to PEG</td>
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<td>Side effects</td>
<td>More diarrhea seen in PEG group but no dehydration</td>
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<td></td>
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<td></td>
<td>Compliance</td>
<td>None refused PEG whereas 33% refused to take milk of magnesia</td>
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<td>Citation, country</td>
<td>Study group</td>
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<td>Loening-Baucke et al (2004), USA 6</td>
<td>Case series (level 4)</td>
<td>Stool frequency</td>
<td>Increased from $3.7 \pm 3.2$ wk to $12.4 \pm 7.0$ wk in the initial 4 months and then $8.6 \pm 3.1$ wk over long term. Also significant improvement in signs and symptoms of constipation. Constipation relieved in 85% with short-term and 91% with long-term therapy.</td>
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<td>Demonstrated the efficacy, tolerability and safety of PEG use for constipation in &lt;2 year olds</td>
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<td>Effective dose</td>
<td>Average effective dose was 1.1 g/kg/day over short term and 0.8 g/kg/day over long term.</td>
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<td>Adverse effects</td>
<td>5 had diarrhoea which improved on decreasing the dose. PEG was not stopped in anyone.</td>
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<tr>
<td>Michail et al (2004), USA 7</td>
<td>Case series (level 4)</td>
<td>Dose</td>
<td>Mean initial dose was 0.88 g/kg/day. Mean effective maintenance dose was 0.78 g/kg/day.</td>
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<td>Demonstrated the efficacy, tolerability and safety of PEG use for constipation in &lt;18 month olds</td>
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<td>Efficacy</td>
<td>Mean stool frequency increased from $2.2 \pm 0.1$ wk to $8.4 \pm 2.5$ wk ($p&lt;0.001$). Mean stool consistency score increased from 1.7±0.5 to 3.8±0.8 ($p&lt;0.001$). PEG relieved constipation in 97.6% of patients.</td>
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<td>Side effects</td>
<td>1 (3.6%) infant had flatulence and 4 (14.3%) had transient diarrhoea which resolved after dose adjustment.</td>
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<td>Pashankar et al (2003), USA 8</td>
<td>Case series (level 4)</td>
<td>Efficacy in constipation</td>
<td>Average dose 0.78 g/kg/day. Stool frequency increased from 2.9±0.3/wk to 9.9±0.7/wk ($p&lt;0.001$). Stool consistency score (from 1 to 5) increased from 1.4±0.1 to 3.1±0.1 ($p&lt;0.001$). Also significant improvement in signs and symptoms of constipation.</td>
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<td>Efficacy and compliance over long term was studied</td>
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<td>Efficacy in constipation and encopresis</td>
<td>Average dose 0.69 g/kg/day. Stool frequency increased from 3.0±0.5/wk to 12.5±1.5/wk ($p&lt;0.001$). Stool consistency score (from 1 to 5) increased from 1.4±0.1 to 3.1±0.1 ($p&lt;0.001$). Scaled events decreased from 11.0±1.6/wk to 1.8±0.5/wk ($p&lt;0.001$). Also significant improvement in signs and symptoms of constipation.</td>
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<td>Efficacy in constipation and encopresis</td>
<td>Good daily compliance in 93%. Average dose 0.69 g/kg/day. Stool frequency increased from 3.0±0.5/wk to 12.5±1.5/wk ($p&lt;0.001$). Stool consistency score (from 1 to 5) increased from 1.4±0.1 to 3.1±0.1 ($p&lt;0.001$). Scaled events decreased from 11.0±1.6/wk to 1.8±0.5/wk ($p&lt;0.001$). Also significant improvement in signs and symptoms of constipation.</td>
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<tr>
<td>Erickson et al (2003), USA 9</td>
<td>Case series (level 4)</td>
<td>Stool frequency</td>
<td>Increased from $0.42 \pm 0.2$/day to $1.25 \pm 0.42$/day ($p=0.0001$).</td>
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<td>Addressed efficacy in those with constipation and resulting disorders in micturition</td>
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<td>Dysfunctional voiding</td>
<td>18 (39%) children became dry, 26 (56.5%) had decreased wetting and 2 showed no improvement</td>
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<td>Voided volume</td>
<td>Increased from 146 ml to 210 ml ($p=0.0001$)</td>
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<td>Post-void residual volume</td>
<td>Post-void residual volume decreased from 92 ml to 48 ml ($p&lt;0.0001$)</td>
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<td>Side effects</td>
<td>9/46 had diarrhoea and 1 stopped treatment</td>
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<tr>
<td>Pashankar et al (2003), USA 10</td>
<td>Case series (level 4)</td>
<td>Clinical adverse effects</td>
<td>Diuretic-related diarrhoea in 10%, flatulence and bloating in 6% and abdominal pain in 2%. Nine subjects had transient mild elevation in ALT and 3 in AST which self-corrected in 11 later. Thought to be unrelated to PEG.</td>
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<td>Long-term compliance and safety for PEG studied</td>
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<td>Biochemical changes</td>
<td>Nine subjects had transient mild elevation in ALT and 3 in AST which self-corrected in 11 later. Thought to be unrelated to PEG.</td>
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<td>Patient acceptance</td>
<td>Good daily compliance in 90%. Caretaker reported improvement in 91% and liked by 73% of children</td>
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Are antiemetics helpful in young children suffering from acute viral gastroenteritis?

Report by
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doi: 10.1136/adc.2004.064972

An 18 month old female is brought to the emergency department by her mother. She has been suffering from repeated vomiting and diarrhoea for the past 24 hours. Over the past eight hours she has vomited approximately 12 times. The vomitus has not contained any bile or blood. The little girl appears mildly dehydrated. Her stool tests positive for rotavirus. You wonder whether administration of an antiemetic may lessen her symptoms and increase the likelihood that oral rehydration therapy will be successful.

Structured clinical question
In an 18 month old girl with rotavirus gastroenteritis [patient], does the administration of antiemetic medication [intervention] decrease vomiting and increase the likelihood that oral rehydration therapy will be successful [outcome]?

Search strategy and outcome
Secondary sources: none.

Medline 1966–July, 2004 using OVID interface: ondansetron OR promethazine OR metoclopramide OR antiemetics AND exp rotavirus infections OR exp Norwalk virus OR exp gastroenteritis OR exp enteritis OR exp transmissible gastroenteritis virus OR exp rotavirus

Limits: human, English language, all infant (birth to 23 months) or preschool child (2 to 5 years) or child (6 to 12 years).
No systematic reviews. Seventy papers were identified, four of which were relevant.
See table 2.

Commentary
No study expressly answered the question as to whether antiemetics lessen the vomiting associated specifically with rotavirus gastroenteritis infection in children and increase the likelihood that oral rehydration therapy will be successful. In the one study in which the authors attempted to identify the cause of gastroenteritis,3 approximately half of the enrolled children were suffering from rotavirus gastroenteritis. It is reasonable to assume that at least similar numbers of children in the other studies were suffering from rotavirus infection.

In one study,2 oral ondansetron (1.6–4 mg/dose depending on the child’s age) or placebo was administered in the emergency department and then every eight hours for up to two days. Compared to the controls, children that received ondansetron experienced less vomiting while they were in the emergency department, were less likely to require intravenous fluid therapy, and were less likely to be admitted to the hospital. In another study,1 a single dose of intravenous ondansetron (0.15 mg/kg) or placebo was given in the emergency department. All of the children in this study also received intravenous fluids. The children who received ondansetron had significantly less vomiting in the emergency department than did the children who received placebo. Hospitalisation rates were comparable in the two groups; however when the authors excluded children who had a serum CO2 less than 14 mEq/l or had received intravenous fluids prior to their emergency room visit, those who received ondansetron were significantly less likely to be admitted to the hospital than were children who were treated with placebo.

Cubeddu and colleagues3 showed that in children hospitalised with gastroenteritis, a single dose of intravenous ondansetron (0.3 mg/kg) decreased the frequency of vomiting over the subsequent 24 hours compared to a single dose of metoclopramide (0.3 mg/kg) or placebo. Van Egan and colleagues4 showed that in children hospitalised with gastroenteritis, 30 mg domperidone suppositories decreased the amount of vomiting compared to 10 mg metoclopramide suppositories or placebo. In both of these two studies, metoclopramide was not superior to placebo.

In these four studies comprising 358 patients, no serious side effects were associated with the administration of...
Table 2 Antiemetics in acute viral gastroenteritis

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study group</th>
<th>Study type</th>
<th>Outcome</th>
<th>Key results</th>
<th>Comments</th>
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<tr>
<td>Reeves et al (2002)</td>
<td>107 children, age 1 month to 22 years who presented to an ED who had experienced at least three episodes of vomiting in the previous 24 hours thought to be secondary to an acute gastroenteritis and required intravenous fluids. Patients were excluded if they had received any antiemetic therapy within 72 hours of enrolment, had a history of hepatic disease or had diarrhoea lasting more than 7 days.</td>
<td>Double blind RCT</td>
<td>Primary outcomes: frequency of vomiting episodes after drug administration, and the need for hospitalisation. Secondary outcomes: duration of vomiting after drug administration, number and duration of diarrhoea symptoms, frequency of return visits to an urgent or emergency care centre, need for readministration of intravenous fluids, and need for later hospital admission.</td>
<td>38 (70%) of the 54 patients in the group who received ondansetron and 27 (51%) in the group that received placebo had complete cessation of vomiting (p = 0.04). Fourteen patients (26%) who received ondansetron and 16 patients (30%) who received placebo were hospitalised (p &gt; 0.05).</td>
<td>The study was supported by a grant from Glaxo Wellcome Inc. who manufacture ondansetron. The majority of children studied were less than 4 years of age. No testing was done to determine the cause of gastroenteritis.</td>
</tr>
<tr>
<td>Cubeddu et al (1997)</td>
<td>36 children ages 6 months to 8 years diagnosed with acute gastroenteritis with associated vomiting who had vomited twice within one hour. Patients were excluded if they were severely dehydrated, had a rectal temperature greater than 39°C, had experienced seizures, or had received any parenteral antiemetic medication in the six hours prior to the study.</td>
<td>Double blind RCT</td>
<td>Frequency of vomiting over the 24 hours after treatment.</td>
<td>The number of vomiting episodes was significantly less in the children who received ondansetron (mean = 2) than in controls (mean = 5). There was no statistically significant difference between children treated with metoclopramide or placebo. 58% of children who received ondansetron experienced no vomiting as compared to 17% of controls. There was no statistically significant difference between children treated with metoclopramide or placebo.</td>
<td>The study was supported by Glaxo Wellcome Research and Development who manufacture ondansetron. 47% of children enrolled had rotavirus enteritis, 11% had adenovirus enteritis, and 31% had bacterial enteritis. All 36 children completed the study. At entry, children in the placebo group were somewhat better hydrated and somewhat older than children in both treatment groups. There was no difference in the number or type of adverse events in the three groups.</td>
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<td>Ramsook et al (2002)</td>
<td>145 children ages 6 months to 12 years who presented to an ED due to with or without diarrhoea thought to be secondary to gastroenteritis and had vomited at least five times during the preceding 24 hours and had not received any antiemetics. Patients were excluded if they had any chronic illnesses, possible appendicitis, urinary tract infection, or, severe gastroenteritis requiring immediate intravenous fluid resuscitation.</td>
<td>Double blind RCT</td>
<td>Primary outcomes: frequency of emesis during the 48 hours after enrolment and rates of intravenous fluid administration. Secondary outcomes: hospital admission rates and frequency of diarrhoea.</td>
<td>The rank sum of vomiting episodes while in the ED was significantly lower in the group who received ondansetron (p = 0.001). During the 48 hours of follow up, the median number of episodes of vomiting were not significantly different in the two groups. A lower proportion of patients receiving ondansetron required intravenous fluids (p = 0.015). The admission rate was lower in the patients receiving ondansetron (p = 0.007). Children receiving ondansetron had significantly more diarrhoea in the 48 hour follow up period than did controls. The children who received ondansetron were more likely to return to the ED than were controls (p = 0.047).</td>
<td>The study was supported in part by a grant from GlaxoWellcome Research and Development who manufacture ondansetron. The majority of children studied were less than 4 years of age. No testing was done to determine the cause of gastroenteritis. 120 children were available for follow up at 24 hours and 113 were available for follow up at 48 hours.</td>
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ondansetron, metoclopramide, or domperidone; however only 140 patients received ondansetron, 32 received metoclopramide, and 20 received domperidone, and follow up was limited to no more than seven days. In the study by Cubeddu and colleagues,1 hospitalised children who received ondansetron or metoclopramide experienced more episodes of diarrhoea during the 24 hour study period than did children who received placebo. Similarly, in the study by Ramsook and colleagues,2 children who received ondansetron during the 48 hour study period than did children who received placebo. In two of the studies,2 3 children who received ondansetron experienced more diarrhoea than did children who received placebo.

### REFERENCES


### CLINICAL BOTTOM LINE

- There is currently insufficient evidence to justify the use of oral or intravenous ondansetron in children suffering from acute viral gastroenteritis. A large, well constructed prospective study is needed to answer this question.
- Ondansetron given intravenously (0.15–0.3 mg/kg/dose) or orally (1.2–4 mg/dose given every eight hours) probably decreases vomiting in children suffering from viral gastroenteritis.
- Serious complications appear to occur in less than 1% of children given ondansetron, but studies in gastroenteritis are limited.
- Ondansetron given intravenously (a single dose of 0.15–0.3 mg/kg) or orally (1.2–4 mg/dose given every eight hours) may decrease the need for hospitalisation in children suffering from vomiting associated with acute viral gastroenteritis.
- Metoclopramide given intravenously or as a suppository does not decrease vomiting in children suffering from viral gastroenteritis.

### Should acyclovir be prescribed for immunocompetent children presenting with chickenpox?

**Report by**

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doi: 10.1136/adc.2005.072215

A 4 year old child is brought to the emergency department by her mother because of a rash that has developed over the preceding 24 hours. The rash is that of uncomplicated chickenpox infection and the history gives a good story of recent contact. The child has no medical history of note and is not immunocompromised. You wonder whether the prescribing of oral acyclovir would reduce the disease severity and duration compared to symptomatic control only.

### Structured clinical question

In uncomplicated chickenpox infection in immunocompetent children (patient) is oral acyclovir (intervention) beneficial in reducing severity and duration of infection (outcome)?

### Search strategy and outcome


Cochrane “acyclovir and chickenpox”.

The Medline search found 14 papers. Papers were excluded if they had no placebo group, which resulted in three relevant papers. These three papers have since been subject to a systematic review by the Cochrane Review Group. The review
was first published in 1999 with the most recent substantive amendment made in February 2004.

See table 3.

**Commentary**

Chickenpox (varicella) remains a common and highly contagious childhood illness among immunocompetent children. Although generally self-limiting, the infection usually presents with an itchy vesicular rash over the trunk and face, fever, and mild systemic upset. Disease complications include secondary bacterial infection of cutaneous lesions, encephalitis, cerebellar ataxia, pneumonia, and otitis media. The economic burden is thought to come from the time taken off work by the child’s caregiver.

All three papers were randomised double blind placebo controlled trials carried out in the USA. Between them they looked at 988 patients aged between 2 and 18 years with either clinical or laboratory diagnoses of varicella.

Although the number of days to no new lesions and number of days to reduction of fever were reduced by one day in the acyclovir groups, the findings that one could consider to be more clinically relevant were less definite.

Reported adverse effects were similar in both groups and there was no significant difference between the treatment groups with respect to all skin, central nervous system, and respiratory complications arising from chickenpox infection.

Balfour and colleagues showed that the efficacy of acyclovir improves if treatment is initiated within 24 of rash onset, which in practical terms is a diagnostic window often difficult to achieve. Although Balfour et al also show that initiating treatment within 48 hours has greater benefit than 72 hours, one may ask oneself if the modest benefits in outcome, when weighed against the strict compliance required for four times daily medication over five days are of clinical worth.

Concerns have been raised regarding the development of resistance to acyclovir. The Cochrane Review concluded that there is evidence to suggest that strains of varicella resistant to acyclovir do not occur.

There is no published evidence to show a positive outcome in cost-benefit analysis and the Cochrane Review showed no reduction in the number of days missed from school between the treatment groups.

Possible issues with the studies were that all three had pharmaceutical sponsorship and other than the study of Dunkle and colleagues, they comprised relatively small patient numbers.

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**Table 3 Use of acyclovir in chickenpox**

<table>
<thead>
<tr>
<th>Citation, country</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>Klassen et al9</td>
<td>988 children aged between 2 and 18 years as per three studies in table below</td>
<td>Cochrane Systematic Review (level 1a)</td>
<td>Number of days to no new lesions, number of days to no fever, maximum number of lesions, days to relief of itching, complication rate</td>
<td>2 of 3 studies showed statistically significant reduction in days to no new lesions, days to relief of itching and reduction of maximum number of lesions. Days to no fever reduced in all studies. Numerous adverse reactions noted in both groups but no significant difference between groups regarding complications arising from varicella</td>
<td>Meta-analysis not done due to small number of studies and their different study populations</td>
</tr>
<tr>
<td>Balfour et al, USA1</td>
<td>105 children, mean age 8.05 years with laboratory confirmed varicella. Randomised to age and weight related dose of acyclovir v placebo</td>
<td>Randomised, placebo controlled double blind trial (level 1b)</td>
<td>Time to reduction of fever and cessation of itching, number of skin lesions, time to cutaneous healing</td>
<td>Acyclovir group: defervesced sooner (median 1 day v 2 days; p=0.001), experienced onset of cutaneous healing sooner (median, 2 days v 3 days; p=0.002), and had fewer skin lesions (median, 500 v 336; p=0.02), no change in complication rate (10% v 13.5%)</td>
<td>Quality score (Jadad scale) = 4 Pharmaceutical sponsorship, inadequate discussion of withdrawn patients</td>
</tr>
<tr>
<td>Dunkle et al, USA4</td>
<td>815 children, mean age 5.18 years with clinically diagnosed varicella. Randomised to weight related dose of acyclovir v placebo</td>
<td>Multicentre, double blind placebo controlled trial (level 1b)</td>
<td>Maximum of lesions, number with &gt;500 lesions, residual lesions at 28 days</td>
<td>Acyclovir group: had fewer lesions (mean 294 v 347; p&lt;0.001), smaller proportion had &gt;500 lesions (21% v 38%; p&lt;0.001), accelerated progression to crusting and healing plus fewer residual lesions at 28 days. No significant difference in disease complications</td>
<td>Quality score (Jadad scale) = 3 Pharmaceutical sponsorship, poorly described methods of randomisation and double blinding</td>
</tr>
<tr>
<td>Balfour et al, USA3</td>
<td>68 children, mean age 14.8 years with laboratory confirmed varicella. Randomised to acyclovir 800 mg QDS or placebo</td>
<td>Randomised, placebo controlled double blind trial (level 1b)</td>
<td>Days to max number of lesions and cessation of itching, maximum number of lesions, residual lesions at 28 days</td>
<td>Acyclovir group had reduction in: time to cessation of new lesions (p&lt;0.001), maximum number of lesions (p=0.019), time to defervescence (p=0.045), number of lesions at 28 days (mean 22.7 v 92.7), constitutional illness score (mean 0.5 v 1.4; p=0.05)</td>
<td>Quality score (Jadad scale) = 3 Pharmaceutical sponsorship, poorly described methods of randomisation and double blinding</td>
</tr>
</tbody>
</table>

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**CLINICAL BOTTOM LINE**

- Oral acyclovir shortens time to fever reduction and time to no new lesions by one day but has no effect on complication rates secondary to infection. (Grade A)
- These reductions were only seen if treatment was initiated with 24 hours of rash onset. (Grade B)
- Use of acyclovir should not currently be recommended in immunocompetent children with chickenpox infection. (Grade A)
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REFERENCES

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