

## Translating Best Evidence into Best Care

EDITOR'S NOTE: Journals reviewed for this issue: *Archives of Disease in Childhood*, *Archives of Pediatrics and Adolescent Medicine*, *British Medical Journal*, *Journal of the American Medical Association*, *Journal of Pediatrics*, *The Lancet*, *New England Journal of Medicine*, *Pediatric Infectious Diseases Journal*, and *Pediatrics*. Gurpreet K. Rana, BSc, MLIS, Taubman Medical Library, University of Michigan, contributed to the review and selection of this month's abstracts.

—John G. Frohna, MD, MPH

### Ondansetron reduces vomiting in children with acute gastroenteritis

DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: A systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2008;162:858-65.

**Question** Among children with gastroenteritis, does the use of antiemetic drugs reduce vomiting and decrease the need for further intervention without causing significant adverse effects?

**Design** Systematic review and meta-analysis.

**Data Sources** Computerized databases, reference lists, and expert recommendations.

**Study Selection** Prospective controlled trials evaluating medication use in children with vomiting from gastroenteritis.

**Intervention** Antiemetic drug therapy.

**Outcomes** Emesis cessation, use of intravenous fluid for rehydration, hospital admission, return to care, and medication adverse effects.

**Main Results** The 11 articles that met the inclusion criteria evaluated various antiemetic agents: ondansetron ( $n = 6$ ), domperidone ( $n = 2$ ), trimethobenzamide ( $n = 2$ ), pyrilamine-pentobarbital ( $n = 2$ ), metoclopramide ( $n = 2$ ), dexamethasone ( $n = 1$ ), and promethazine ( $n = 1$ ). Meta-analysis of 6 randomized, double-masked, placebo-controlled trials of ondansetron demonstrated decreased risk of further vomiting (5 studies; relative risk [RR] 0.45; 95% confidence interval [CI], 0.33-0.62; number needed to treat [NNT] = 5), reduced need for intravenous fluid (4 studies; RR, 0.41; 95% CI, 0.28-0.62; NNT = 5), and decreased risk of immediate hospital admission (5 studies; RR, 0.52; 95% CI, 0.27-0.95; NNT = 14). Diarrheal episodes increased in ondansetron-treated patients in 3 studies. Ondansetron use did not significantly affect return to care (5 studies; RR, 1.34; 95% CI, 0.77-2.35).

**Conclusions** Ondansetron therapy decreases the risk of persistent vomiting, the use of intravenous fluid, and hospital admissions in children with vomiting caused by gastroenter-

itis. Future treatment guidelines should incorporate ondansetron therapy for select children with gastroenteritis.

**Commentary** When gastroenteritis makes children vomit, everyone wants it to stop. This systematic review suggests that ondansetron might do just that. DeCamp et al found that ondansetron effectively reduced further emesis, the need for intravenous fluid, and hospitalizations in patients ages 1 month to 22 years who came to the emergency department with acute gastroenteritis. Although 2 earlier reviews concluded that ondansetron was not effective for acute gastroenteritis, this review includes more recent studies that push the verdict in the other direction. By using only randomized, controlled trials, careful quality assessments, and a very thorough literature search, DeCamp et al produced a high-quality meta-analysis for which the results should be reliable and valid. The results were consistent across the studies for the major outcomes of avoiding intravenous fluid and stopping vomiting, but varied more widely for preventing admissions. Readers are cautioned that the studies were all done in emergency departments, so we do not know if ondansetron works as well for children who are less sick or are in outpatient settings. The side effect of diarrhea must also be investigated more carefully. Overall, this is a well-conducted analysis that provides strong evidence that emergency medicine physicians should use ondansetron for this population.

Rachel C. Vreeman, MD, MS  
Indiana University School of Medicine  
Indianapolis, Indiana

### Evidence not persuasive for recommending a combination of ibuprofen and acetaminophen for feverish children

Hay AD, Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. *BMJ* 2008;337:1490-7.

**Question** Among febrile children managed at home, is acetaminophen plus ibuprofen superior to either drug alone

for increasing time without fever and the relief of fever-associated discomfort?

**Design** Randomized, blinded, 3-arm trial.

**Setting** Primary care settings in Bristol, England.

**Participants** A total of 156 children, ages 6 months to 6 years with axillary temperatures of at least 37.8° C and up to 41.0° C.

**Intervention** Advice on physical measures to reduce temperature and the provision of, and advice to give, acetaminophen plus ibuprofen, acetaminophen alone, or ibuprofen alone.

**Outcomes** Primary outcomes were the time without fever (<37.2° C) in the first 4 hours after the first dose was given and the proportion of children reported as being normal on the discomfort scale at 48 hours. Secondary outcomes were time to first occurrence of normal temperature (fever clearance), time without fever over 24 hours, fever-associated symptoms, and adverse effects.

**Main Results** On an intention to treat basis, acetaminophen plus ibuprofen were superior to acetaminophen for less time with fever in the first four hours (adjusted difference 55 minutes, 95% confidence interval 33 to 77;  $P < .001$ ) and may have been as good as ibuprofen (16 minutes,  $-7$  to 39;  $P = 0.2$ ). For less time with fever over 24 hours, acetaminophen plus ibuprofen were superior to acetaminophen (4.4 hours, 2.4 to 6.3;  $P < .001$ ) and to ibuprofen (2.5 hours, 0.6 to 4.4;  $P = .008$ ). Combined therapy cleared fever 23 minutes (2 to 45;  $P = .025$ ) faster than acetaminophen alone but no faster than ibuprofen alone ( $-3$  minutes, 18 to  $-24$ ;  $P = .8$ ). No benefit was found for discomfort or other symptoms, although power was low for these outcomes. Adverse effects did not differ between groups.

**Conclusions** Parents, nurses, pharmacists, and doctors wanting to use medicines to supplement physical measures to maximize the time that children spend without fever should use ibuprofen first and consider the relative benefits and risks of using acetaminophen plus ibuprofen over 24 hours.

**Commentary** Fever is common in children and causes parents to worry. Most febrile children have self-limiting infections and will get better without treatment. But young children who are febrile are usually uncomfortable and miserable. It is standard practice for doctors to recommend, and parents to administer, antipyretic treatment. The 2 most widely used drugs are acetaminophen and ibuprofen. Recently it has become increasingly common for doctors to recommend a combination of both drugs, so this primary care study randomizing feverish young children to either drug alone or a combination of the 2 drugs is timely. The authors report 2 primary outcomes: time without fever in first 4 hours and fever-associated discomfort after 48 hours. The first could be argued to represent a proxy of parental concern, but it is fever-associated discomfort that is the key outcome. And for this outcome, the study is underpowered. One hundred fifty-

six children were recruited and randomized from 1038 potentially eligible participants. Despite this, their results suggest no additional improvement in fever-associated discomfort or activity levels in the combined medication group at 24 hours, 48 hours, and 5 days. Their data confirm that ibuprofen is faster acting and has a longer duration than acetaminophen but that a combination of drugs has little advantage. Of some concern is their report of 31 children in the combined group receiving an overdose of medication even in clinical trial conditions. A larger trial is required to confirm their findings, but for now, I am not persuaded that prescribing a combination of acetaminophen and ibuprofen for the treatment of feverish young children has any advantage over use of either drug alone.

Anthony Hamden, MB ChB, FRCGP, FRCPC  
Oxford University  
Oxford, United Kingdom

## Nicotine nasal spray neither effective nor well-tolerated by adolescent smokers

Rubinstein ML, Benowitz NL, Auerback GM, Moscicki A. A randomized trial of nicotine nasal spray in adolescent smokers. *Pediatrics* 2008;122:e595-e600.

**Question** Among adolescent smokers who wanted to quit smoking, is nicotine nasal spray effective at increasing cessation rates?

**Design** Randomized, open-label, 12-week trial.

**Setting** Five San Francisco Bay Area high schools.

**Participants** Forty adolescents, ages 15 to 18 years of age, who smoked  $\geq 5$  cigarettes daily for at least 6 months.

**Intervention** Participants were assigned to receive either weekly counseling alone (control) for 8 weeks or 6 weeks of nicotine nasal spray along with 8 weeks of counseling.

**Outcomes** Self-reported smoking abstinence, as verified by both expired-air carbon monoxide and salivary cotinine levels.

**Main Results** There was no difference in cessation rates, the number of cigarettes smoked per day, or cotinine levels at 12 weeks. Fifty-seven percent of participants stopped using their spray after only 1 week. The most commonly reported adverse effect was nasal irritation and burning (34.8%), followed by complaints about the taste and smell (13%).

**Conclusions** The unpleasant adverse effects, poor adherence, and consequent lack of efficacy observed in this pilot study do not support the use of nicotine nasal spray as an adjunct to counseling for adolescent smokers who wish to quit.

**Commentary** This is an important and well-designed first study of the effect of nicotine nasal spray (NNS) on adolescent smoking cessation that supports current evidence-based guidelines that nicotine replacement therapy is neither effective nor recommended for adolescents.<sup>1</sup> NNS theoretically

could succeed for adolescents where other forms of nicotine replacement failed. Consistent with adolescent tobacco use patterns, potential benefits of NNS over other forms of nicotine replacement include the following: (1) NNS can be used intermittently, (2) in response to environmental influences, such as smoking to relieve stress, NNS has a relatively fast delivery of nicotine with reinforcing effects, and (3) compared with other forms of nicotine replacement, NNS allows greater self-control and ownership of the intervention, which adolescents prefer. Admirably, this study uses a validated nicotine dependence questionnaire for adolescents, a withdrawal symptom scale, biochemical validation of self-report, and an intention-to-treat analysis. Two noteworthy design limitations exist: First, this is an open-label trial without a placebo group. Second, although originally designed to be an effectiveness study, failure to meet sample size requirements forced the authors to truncate the study for feasibility. These limitations are relatively minor, however, because this study convincingly shows that NNS is not tolerated by adolescents. Although the delivery system holds promise for adolescent smokers, the negative side effects of the spray, in particular burning associated with use, led to such poor adherence that discussion of efficacy is moot. If future NNS preparations are better tolerated, this study deserves replication with adequate power to reexamine the issue of effectiveness for adolescents.

William P. Adelman, MD  
Uniformed Services University of the Health Sciences  
Bethesda, Maryland

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### Continuous glucose monitoring study does not demonstrate benefit in children and adolescents

The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464-76.

**Question** Among patients with type 1 diabetes mellitus, does the use of continuous glucose monitoring result in improved glycemic control?

**Design** Randomized, controlled trial.

**Setting** Multiple centers in the United States.

**Participants** A total of 322 adults and children who were already receiving intensive therapy for type 1 diabetes.

**Intervention** Continuous glucose monitoring or a control group performing home monitoring with a blood glucose meter.

**Outcomes** Change in the glycated hemoglobin level at 26 weeks.

**Main Results** The changes in glycated hemoglobin levels in the 2 study groups varied markedly according to age group ( $P = .003$ ), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change,  $-0.53\%$ ; 95% confidence interval [CI],  $-0.71$  to  $-0.35$ ;  $P < .001$ ). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference,  $0.08$ ; 95% CI,  $-0.17$  to  $0.33$ ;  $P = 0.52$ ) or among those who were 8 to 14 years of age (mean difference,  $-0.13$ ; 95% CI,  $-0.38$  to  $0.11$ ;  $P = .29$ ). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of continuous glucose monitoring averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe hypoglycemia was low and did not differ between the 2 study groups; however, the trial was not powered to detect such a difference.

**Conclusions** Continuous glucose monitoring can be associated with improved glycemic control in adults with type 1 diabetes, but was not effective in children and adolescents.

**Commentary** This is the largest, prospective, individually randomized unblinded controlled trial of continuous glucose monitoring (CGM). Use of CGM was associated with significantly improved glycemic control in adults with type 1 diabetes, but not children or adolescents. Between-group A1C levels fell by a mean of 0.53% in adults. Nonsignificant benefit of CGM was observed in subjects who were 8 to 14 years of age, and no benefit was observed among subjects who were 15 to 24 years of age. Why didn't children and adolescents benefit? The reasons might be related to adherence and to the study's method for randomization. Use of CGM is a tool for directing behavior on the basis of glucose levels. Adherence to a behavioral intervention is necessary for the intervention to be successful.<sup>1</sup> Adherence alone might account for the ranking of results between adults with the greatest compliance (80%) and greatest benefit, compared with children with the second-best compliance (50%) and second best results, and adolescents with the least compliance (33%) least benefit. The study used individual randomization, which is appropriate for a blinded trial, but in an unblinded trial of a behavioral intervention, cluster randomization of study sites is often used to prevent contamination of control subjects from knowledge of the intervention.<sup>2</sup> If control subjects learn about benefits of using CGM at the investigator's office, then they might monitor their glucose more frequently and artifactually improve their control. This behavior could improve the A1C outcome for controls and wash out the between-group benefit of the CGM intervention. Indeed, in this study the children and adolescent control subjects both had at least a

0.21% improvement in A1C, suggesting possible contamination of control subjects in this study.

David C. Klonoff, MD  
Mille-Peninsula Health Services  
San Mateo, California

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### Clinical dehydration scale appears valid, but its impact on clinical outcomes is not clear

Goldman RD, Friedman JN, Parkin PC. Validation of the clinical dehydration scale for children with acute gastroenteritis. *Pediatrics* 2008;122:545-9.

**Question** Among children who present with acute gastroenteritis to an emergency department, is a clinical dehydration scale able to validly predict length of stay and need for intravenous fluids?

**Design** Prospective observational study.

**Setting** Emergency department at a large pediatric tertiary center in Canada.

**Participants** A total of 205 children, aged 1 month to 5 years, with symptoms of acute gastroenteritis.

**Outcomes** Length of stay, proportion of children receiving intravenous fluid rehydration, and proportions of children with abnormal serum pH values or bicarbonate levels.

**Main Results** The distribution of severity categories was as follows: no dehydration (score of 0),  $n = 117$  (57%); some dehydration (score of 1-4),  $n = 83$  (41%); moderate/severe dehydration (score of 5-8),  $n = 5$  (2%). The 3 dehydration categories were significantly different with respect to the validation hypotheses (length of stay, mean  $\pm$  SD: none,  $245 \pm 181$  minutes; some,  $397 \pm 302$  minutes; moderate/severe,  $501 \pm 389$  minutes; treatment with intravenous fluids: none,  $n = 17$ , 15%; some,  $n = 41$ , 49%; moderate/severe,  $n = 4$ , 80%; number of vomiting episodes in the 7 days before the

emergency department visit: none,  $8.4 \pm 7.7$  episodes; some,  $13 \pm 10.7$  episodes; moderate/severe,  $30.2 \pm 14.8$  episodes).

**Conclusions** The clinical dehydration scale and the 3 severity categories were valid for a prospectively enrolled cohort of patients who were assessed in this tertiary emergency department. The scoring system was valuable in predicting a longer length of stay and the need for intravenous fluid rehydration for children with symptoms of acute gastroenteritis.

**Commentary** The authors' primary objective was to validate their clinical dehydration scale (CDS) in a prospective cohort of children with acute gastroenteritis. The scale consists of 4 physical examination variables: general appearance, eyes (sunken or not), moistness of mucous membranes, and presence of tears. Each variable is scored from 0 to 2 points. The results of this study seem to suggest that children with more than "none" of these clinical signs of dehydration may have a longer length of stay in the emergency department and may receive intravenous fluids. Although not unexpected, it is good to see that an increased CDS corresponds with increased use of emergency department resources. However, as we look to use this score in clinical practice, we must consider a few caveats. First, the use of "decreased tears" as a criterion is suspect, because not every child cries during their triage assessment. Second, the clinical utility of the CDS is not clear. The strength of the correlation between the CDS and the outcomes is not great enough to make me want to rely solely on these 4 findings. Third, the authors may have minimized the reasons for the variability in the length of stay or the need for intravenous fluids. The low number of children in the moderate/severe dehydration group makes the need for precision in determining outcomes even more important. Finally, the authors state that 5 children were admitted, but they do not report admission as an outcome variable (and they do not identify which CDS category these children were in, nor their length of stay). As with all clinical prediction rules, the most important evidence will come from future studies that assess its impact on practice.

Greg Rebella, MD  
University of Wisconsin American Family Children's Hospital  
Madison, Wisconsin