Use of Antiemetic Agents in Acute Gastroenteritis

A Systematic Review and Meta-analysis

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Objective: To perform a systematic review and meta-analysis to determine whether taking antiemetic drugs reduces vomiting and decreases the need for further intervention in children with gastroenteritis without causing significant adverse effects.

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.

Main Outcome Measures: Emesis cessation, use of intravenous fluid for rehydration, hospital admission, return to care, and medication adverse effects.

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

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A CUTE GASTROENTERITIS IS A common illness of childhood that accounts for more than 1.5 million outpatient visits in the United States annually and 13% of hospitalizations for children younger than 5 years.1,2 Although death due to gastroenteritis in the United States is rare, diarrhea and dehydration are common causes of death in developing countries.1,3

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In addition, many physicians believe that vomiting is a contraindication to ORT. Physicians who provide care to pediatric patients in the emergency department (ED) consistently favor intravenous fluid (IVF) for mild or moderate dehydration when vomiting is the major symptom.4,5 At least half of all physicians caring for children with gastroenteritis report prescribing antiemetic agents, and 10% of children with gastroenteritis who undergo outpatient care fill a prescription for an antiemetic drug.6,7

Promethazine was the most commonly prescribed antiemetic agent for children as recently as 2003, with metoclopramide, trimethobenzamide, and prochlorperazine prescribed less frequently.6,7 However, widespread use of these medications became controversial because of reports of important adverse effects, including sedation and extrapyra-
midal reactions. These concerns caused the Food and Drug Administration to recommend against the use of promethazine in children younger than 2 years, and many pediatricians have stopped using these antiemetic medications in all children.

5-Hydroxytryptamine antagonists, such as ondansetron, are a class of antiemetic drugs that have few adverse effects and that have been safely used in children as young as 1 month old for the treatment of postoperative or chemotherapy-associated nausea and vomiting. Several recent studies have also evaluated the use of ondansetron in children with vomiting from gastroenteritis. All of these studies report a decrease in vomiting; however, the effect on other important outcomes, such as IVF use and hospital admission, has been inconsistent.

We conducted a systematic review followed by a meta-analysis to determine whether antiemetic drug use in children with gastroenteritis provides symptomatic relief and improves other clinically significant outcomes, and whether important adverse effects result from using these medications.

## METHODS

### STUDY IDENTIFICATION AND SOURCES

We used a comprehensive search strategy to identify prospective English-language studies that evaluated the use of antiemetic medications compared with controls in children with vomiting from gastroenteritis. A medical librarian designed and guided the primary search of the MEDLINE database via PubMed. Three of us (L.R.D., J.S.B., and M.J.S.) reviewed all the titles and pertinent abstracts from the primary search. This search was supplemented by medication-specific searches of PubMed by 1 of us (M.J.S.). The combined PubMed searches are available from the authors.

**Figure 1** details the results of additional searches in the Cochrane Central Register of Controlled Trials, the Alternative Medicine Database, and the International Pharmaceutical Abstracts Database. In an attempt to identify and minimize publication bias, we also searched the Clinical Trials Registry (at http://clinicaltrials.gov) to identify unreported trials. We reviewed the reference lists of all potential articles and important reviews and contacted experts in the field to provide additional published studies if available. Articles were included for full review if any author thought that the study might provide primary data addressing the pharmacologic treatment of vomiting from gastroenteritis in children.

### QUALITY ASSESSMENT AND DATA EXTRACTION

The journal of publication and author names were masked for each included study during full review by 1 of us (N.D.). Two of the other 3 authors then independently assessed the quality of each included study. The article by Roslund et al was initially published in abstract form and was not assigned a quality score during preliminary work on the systematic review. When the full study was later published, a nonmasked quality score was independently assigned by 2 of us (J.S.B. and M.J.S.).

A methodological quality assessment checklist created by Downs and Black was used as the primary assessment tool. An evidence report from the Agency for Healthcare Research and Quality previously identified this as 1 of only 2 tools that included all the key domains of methodological quality and that could be used for empirical and observational studies. Systematic reviews and meta-analyses may vary greatly depending on the quality assessment tool used to stratify studies. For this reason, each article underwent a second quality assessment using a tool that was constructed by means of a Delphi consensus process among epidemiologists. Any differences in quality ranking between reviewers were resolved by discussion among all the authors until consensus was achieved.

Data were extracted independently by 2 of 3 authors (L.R.D., J.S.B., and M.J.S.) for each article using a standardized form (available from the authors). Data and methods extracted included patient number, age, inclusion and exclusion criteria, study location, patient assignment, masking, intervention and control, standard treatments received by both groups, primary and secondary outcomes, follow-up, and adverse events.

### STATISTICAL ANALYSIS

We created 2 × 2 tables from the published data for the dichotomous outcomes of further emesis in the ED, failed ORT with resultant IVF use, admission to the hospital from the ED, admission to the hospital at any point during follow-up, and return to...
The 6 studies of ondansetron included 745 children with vomiting and a clinical diagnosis of gastroenteritis. Two studies,15,16 also required dehydration for inclusion, 1 also required ORT failure (emesis or refusal to take oral fluids),18 and 1 required both dehydration and ORT failure.13 In all the studies, only 1 dose of ondansetron was administered during the study period, except that by Ramsook et al,15 which provided families with additional doses for home use. Route of administration and dosing varied across studies. Of the studies using intravenous ondansetron, 2 used a dose of 0.15 mg/kg,13,14 whereas Cubeddu et al17 used a dose of 0.3 mg/kg. In studies of oral ondansetron, Freedman et al16 and Roslund et al18 used similar weight-based dosing ranging from 2 to 8 mg, and Ramsook et al15 used age-based dosing ranging from 1.6 to 4.0 mg.

QUALITY ASSESSMENT

The quality of included studies was highly variable, with Downs scores ranging from 8 to 26 of a maximum of 31 and Delphi scores ranging from 2 to 9 of a maximum of 9 (Table). There was a high degree of correlation in the quality assessment of the 2 scores (Spearman \( r = 0.91 \)). The ondansetron studies were the most recently published (1996, 2002-2007) and achieved the highest-quality ratings.13-18

OUTCOMES WITH ONDANSETRON

Hospital Admission

Five trials of ondansetron were conducted in the ED and included hospital admission as an outcome (n=662).13-16,18 Patients who received ondansetron had a statistically significant decrease in risk of hospital admission. In children in the ondansetron group, the risk of admission during the initial ED visit was 7.5%, whereas in the placebo group the AR was 14.6% (RR, 0.52; 95% CI, 0.27-0.95) (Figure 2). The calculated NNT predicts that 14 children would need to be treated with ondansetron to prevent 1 child from being admitted to the hospital (95% CI, 9-44).

IVF Administration

Four included studies15-18 evaluated the use of IVF (n=489). Indications for IVF varied by study and included persistent emesis, refusal to drink, and persistent or worsening dehydration. There was a statistically significant reduction in the RR of IVF use for patients who received ondansetron vs placebo (AR, 13.9% vs 33.9%; RR, 0.41; 95% CI, 0.28-0.62) (Figure 3). The cumulative NNT to prevent IVF use was 5 (95% CI, 4-8).

Cessation of Vomiting in the ED

Four studies13-16 reported whether patients continued to have emesis in the ED after administration of the study drug, and 1 author18 provided unpublished data. Using data from 659 participants, the RR for vomiting after receiving ondansetron compared with placebo was 0.45 (95% CI, 0.33-0.62; AR, 16.9% vs 37.8%) (Figure 4). The NNT with ondansetron to stop 1 child from experiencing further emesis in the ED was 5 (95% CI, 4-7).

Return to Care

Five included studies13-16,18 assessed whether patients returned to outpatient care during study follow-up (n=612). The combined percentage of patients without follow-up data was 8.5%, with no difference between the ondansetron and placebo groups (8.4% and 8.6%, respectively; \( z \) test, \( P = .92 \)). The RR of a return visit after ondansetron use did not differ between the ondansetron and placebo groups (RR, 1.34; 95% CI, 0.77-2.35). Three studies14,16,18 reported whether children discharged from the ED were admitted during follow-up, and 1 study13 supplied this information with original unpublished data. The RR of admission at any point...
Table. Summary of Included Studies Evaluating the Efficacy of Antiemetic Agents in Acute Gastroenteritis

<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>No. of Patients</th>
<th>Age Range</th>
<th>Inclusion Criteria</th>
<th>Antiemetic Agent</th>
<th>Route</th>
<th>Outcomes</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedman et al,16 2006</td>
<td>ED</td>
<td>214</td>
<td>6 mo-10 y</td>
<td>GE with mild to moderate dehydration and vomiting in the preceding 4 h</td>
<td>Ondansetron</td>
<td>PO</td>
<td>Vomiting episodes, receipt of IVF, and admission to the hospital</td>
<td>1-2 wk</td>
</tr>
<tr>
<td>Reeves et al,14 2002</td>
<td>ED</td>
<td>107</td>
<td>1 mo-22 y</td>
<td>GE and vomiting with IV rehydration</td>
<td>Ondansetron</td>
<td>IV</td>
<td>Vomiting episodes, hospital admission, duration of vomiting, diarrheal episodes, and return to ED</td>
<td>5-7 d</td>
</tr>
<tr>
<td>Roslund et al,18 2007</td>
<td>ED</td>
<td>106</td>
<td>1-10 y</td>
<td>GE with failed oral rehydration attempt in ED</td>
<td>Ondansetron</td>
<td>PO</td>
<td>Vomiting episodes, receipt of IVF, hospital admission, diarrheal episodes, and return to ED</td>
<td>1 wk</td>
</tr>
<tr>
<td>Stork et al,13 2006</td>
<td>ED</td>
<td>137</td>
<td>6 mo-12 y</td>
<td>GE, recurrent emesis, mild to moderate dehydration, and failed oral hydration</td>
<td>Ondansetron and dexamethasone</td>
<td>IV</td>
<td>Hospital admission, ORT tolerance, and degree of dehydration</td>
<td>1 and 2 d</td>
</tr>
<tr>
<td>Ramsook et al,15 2002</td>
<td>ED</td>
<td>145</td>
<td>6 mo-12 y</td>
<td>GE with recurrent vomiting in the preceding 24 h</td>
<td>Ondansetron</td>
<td>PO</td>
<td>Vomiting episodes, receipt of IVF, hospital admission, and diarrheal episodes</td>
<td>24 h</td>
</tr>
<tr>
<td>Cubeddu et al,17 1997</td>
<td>Inpatient (Venezuela)</td>
<td>36</td>
<td>6 mo-8 y</td>
<td>Hospitalized with GE and repeated emesis within 1 h</td>
<td>Ondansetron and metoclopramide</td>
<td>IV</td>
<td>Vomiting episodes and ORT failure</td>
<td>24 h</td>
</tr>
<tr>
<td>Tibbs,23 1969</td>
<td>Private pediatric clinic</td>
<td>60</td>
<td>&gt;14 wk</td>
<td>Vomiting due to GE, pharyngitis, or tonsillitis</td>
<td>Pyrilamine-pentobarbital and trimethobenzamide HCl</td>
<td>PR</td>
<td>Vomiting episodes</td>
<td>24 h</td>
</tr>
<tr>
<td>Tibbs,24 1968</td>
<td>Private pediatric clinic</td>
<td>60</td>
<td>4 mo-8 y</td>
<td>Persistent vomiting</td>
<td>Pyrilamine-pentobarbital and promethazine HCl</td>
<td>PR</td>
<td>Vomiting episodes</td>
<td>12 h</td>
</tr>
<tr>
<td>Van Eygen et al,19 1979</td>
<td>Inpatient</td>
<td>60</td>
<td>2-6 y</td>
<td>GE and vomiting</td>
<td>Domperidone and metoclopramide</td>
<td>PR</td>
<td>Need for additional medication and rating of symptom relief</td>
<td>2 h</td>
</tr>
<tr>
<td>Dhondt et al,20 1978</td>
<td>Inpatient</td>
<td>49</td>
<td>8 mo-10 y</td>
<td>Hospitalized with severe vomiting GE with vomiting within previous 2 h</td>
<td>Domperidone</td>
<td>PR</td>
<td>Rating of symptom relief</td>
<td>24 h</td>
</tr>
<tr>
<td>Ginsburg and Clahsen,21 1980</td>
<td>Academic pediatric clinic</td>
<td>49</td>
<td>1-17 y</td>
<td>Vomiting due to GE and vomiting within previous 2 h</td>
<td>Trimethobenzamide HCl</td>
<td>PR</td>
<td>Vomiting episodes and rating of nausea relief</td>
<td>24 h</td>
</tr>
</tbody>
</table>

Abbreviations: ED, emergency department; GE, gastroenteritis; HCl, hydrochloride; IV, intravenous; IVF, intravenous fluid; ORT, oral rehydration therapy; PO, by mouth; PR, per rectum.

a The maximum score possible was 31.
b The maximum score possible was 9.

Figure 2. The relative risk (RR) of hospital admission in ondansetron-treated patients. The size of each black box is proportional to the sample size of the trial. Horizontal bars indicate 95% confidence intervals (CIs); white diamond, the pooled estimate; the peak of the diamond, the point estimate; and the width of the diamond, 95% CI.
during the illness, not just at initial presentation to the ED, was not significantly different between initial group assignments (RR, 0.69; 95% CI, 0.43-1.11).

Adverse Events

Five studies documented episodes of diarrhea after study drug administration. These data could not be combined owing to variation in length of follow-up and documentation of diarrheal episodes. Overall, 3 studies reported increased diarrhea in the ondansetron group either in the ED or during follow-up. Freedman et al reported a statistically significant increase in diarrhea during the ED stay in patients treated with ondansetron but did not evaluate the incidence of diarrhea during follow-up. Ramsook et al did not detect a difference in diarrheal episodes during the ED stay but reported a statistically significant increase in diarrheal episodes in the 48 hours after ED discharge. More diarrheal episodes were also reported in the 24 hours after study drug administration in the ondansetron group by Cubeddu et al. Five to 7 days after ED discharge, neither Roslund et al nor Reeves et al detected a difference in diarrheal episodes among study groups. In summary, although an increase in diarrhea was noted in ondansetron-treated patients up to 48 hours after administration, no difference in frequency was detected beyond that time. No other adverse event was systematically evaluated, and no other adverse effects were common across studies.

OUTCOMES WITH DOMPERIDONE

Two studies of domperidone suppositories for the treatment of vomiting in hospitalized children met the inclusion criteria. These studies reported results for 109 children with vomiting, although enrollment was not limited...
to patients with gastroenteritis. Both studies demonstrated that domperidone decreased the symptoms of nausea and vomiting compared with placebo. Neither trial reported any adverse events or medication adverse effects.

OUTCOMES WITH METOCLOPRAMIDE

Two included studies\textsuperscript{17,25} evaluated metoclopramide as a treatment for vomiting associated with gastroenteritis in 96 hospitalized children. One study\textsuperscript{25} found metoclopramide to be more effective than placebo at reducing symptoms of nausea and vomiting. No adverse events were reported. The second study\textsuperscript{17} found that metoclopramide did not reduce emetic episodes relative to placebo. Reported adverse effects in patients who received metoclopramide included drowsiness, cough, and tremor.\textsuperscript{17}

OUTCOMES WITH TRIMETHOBENZAMIDE

Two included studies\textsuperscript{23,27} evaluated trimethobenzamide hydrochloride suppositories compared with either placebo or pyrilamine-pentobarbital suppositories (n = 109). In children with emesis from a variety of conditions in outpatient settings, trimethobenzamide was no more effective than placebo and was less effective than pyrilamine-pentobarbital. Both studies received low quality scores and were published more than 25 years ago.

OUTCOMES WITH PYRILAMINE-PENTOBARBITAL

Two studies\textsuperscript{23,24} evaluated the pyrilamine-pentobarbital combination compared with either promethazine or trimethobenzamide (n = 120). In both studies, rectal pyrilamine-pentobarbital was superior to the comparison medication at relieving vomiting. Sedation was noted as an adverse effect of pyrilamine-pentobarbital in both studies. These 2 studies were conducted by the same author in a single pediatric practice, were published in regional medical journals, received low quality rankings, did not include placebo groups, and included children with a variety of illnesses that cause emesis.

OUTCOMES WITH OTHER MEDICATIONS

We identified only 1 study\textsuperscript{24} that used promethazine as a treatment for children with vomiting from gastroenteritis. This 60-patient study did not include a placebo group and found promethazine to be less effective than rectal pyrilamine-pentobarbital at relieving nausea and vomiting. No adverse events were attributed to promethazine use.

Dexamethasone was evaluated in 1 study\textsuperscript{13} as a treatment arm along with intravenous ondansetron and placebo (n = 137). Dexamethasone did not lower the risk of further vomiting or hospital admission compared with placebo and was less effective than ondansetron in relieving vomiting.

COMMENT

Gastroenteritis is a common childhood illness, but relatively few experimental studies of medications to treat the associated vomiting exist. In randomized, placebo-controlled studies, children who received ondansetron were less likely to have ongoing vomiting, to be prescribed IVF, or to be admitted to the hospital from the ED. The symptomatic relief and avoidance of invasive therapies are important outcomes that suggest a benefit of ondansetron treatment in moderately ill children with gastroenteritis.

Studies of antiemetic agents other than ondansetron had small sample sizes, were of low methodological quality, and produced inconsistent results. In addition, pyrilamine-pentobarbital is no longer available in the United States, trimethobenzamide rectal suppositories have been removed from the market owing to lack of demonstrated effect, and promethazine carries a black box warning for use in children younger than 2 years.\textsuperscript{9,28,29} Based on the available literature, antiemetic agents other than ondansetron should not be used for outpatients with gastroenteritis.

Studies\textsuperscript{14,15,17,18} of ondansetron consistently demonstrated an increase in diarrhea in treated patients in the 1 to 2 days after administration. The clinical significance of increased diarrhea has not been studied. However, increased diarrhea does not seem to result in increased health care use; the present compiled data did not demonstrate a statistically significant increase in return to care in ondansetron-treated patients. No other adverse effect was commonly detected in patients treated with ondansetron.

The included studies demonstrate variability in the effect of ondansetron to reduce the risk of hospital admission, and the compiled data demonstrate that the ability of single-dose ondansetron in the ED to reduce admission wanes across time. A possible explanation is that the overall clinical course and severity of gastroenteritis are largely determined by the underlying disease or child host and are not necessarily altered by short-term relief of symptoms. In addition, an increase in diarrhea due to ondansetron may contribute to later dehydration. Future research should replicate the home use of ondansetron as in the study by Ramsook et al\textsuperscript{15} to determine whether repeated dosing delivers persistent benefit and consistent reduction in hospital admission.

Two recent reviews\textsuperscript{8,30} of antiemetic medication use in children with vomiting from gastroenteritis reached different conclusions than the present study. A Cochrane review\textsuperscript{8} included only the primary data of Freedman et al,\textsuperscript{16} Ramsook et al,\textsuperscript{15} and Cubeddu et al.\textsuperscript{17} The study by Reeves et al\textsuperscript{14} was excluded owing to the inclusion of patients up to 22 years of age. The studies by Stork et al\textsuperscript{13} and Roslund et al\textsuperscript{18} were published after the Cochrane review was published. A second systematic review by Szajewska et al\textsuperscript{30} did include Reeves et al\textsuperscript{14} but still did not evaluate the studies by Stork et al\textsuperscript{13} and Roslund et al.\textsuperscript{18} The Cochrane review found "some albeit, weak and unreliable evidence" in favor of ondansetron to reduce vomiting from gastroenteritis. Szajewska et al\textsuperscript{30} reported that ondansetron reduces vomiting in the ED and reduces IVF administration, but they still concluded that there was insufficient evidence to recommend its routine use. We believe that the evidence in favor of ondansetron use has increased since these 2 reviews were
published and that we can recommend its use in the ED for dehydrated children at risk for ORT failure.

The Cochrane review did not identify any studies for inclusion that were published in languages other than English. Therefore, the English-language–limited search strategy used in the present review likely did not cause important omissions.

One previously noted criticism of the studies of ondansetron is that clinical decision making in EDs in the United States often favors the use of IVF instead of ORT, making this outcome a controversial marker for antiemetic efficacy. The bias toward IVF is apparent in studies included in this review because emesis during ORT was generally used as a sign of ORT failure and as an indication for IVF. The use of ondansetron for gastroenteritis with emesis is less invasive and probably has a lower risk of adverse effects than IVF use and hospital admission. Because some of the prescribed IVF may have been medically unnecessary for recovery, the decrease in the use of IVF after ondansetron in this study may actually underestimate the reduction that will occur when physicians know that the patient will receive ondansetron and not placebo.

The included ondansetron studies have a variety of limitations that extend to this review. Five of the ondansetron studies were conducted in EDs, and all enrolled moderately ill children; 1 study enrolled only hospitalized children. To our knowledge, no available evidence exists demonstrating the efficacy or utility of ondansetron in individuals with mild disease or in standard office settings. Children who present to primary care offices with gastroenteritis are generally less ill and at lower risk for IVF or hospital admission than children who present to EDs. Consequently, it is unknown whether children with gastroenteritis in primary care offices would benefit from ondansetron therapy. Future studies set in primary care offices should evaluate outcomes such as persistence of emesis, need for IVF, unplanned return to care, ED use, and parental satisfaction.

A second important limitation of the available data is that all the primary studies of ondansetron were completed with assistance from the pharmaceutical company that manufactures the drug (Zofran; GlaxoSmithKline, Research Triangle Park, North Carolina). Previous research has demonstrated that studies with funding from pharmaceutical companies are more likely to have favorable results. Ondansetron is now available in a generic formulation, and future studies should be completed without industry support.

Ondansetron is currently formulated in a solution for injection or infusion, an oral solution, a tablet, and an orally disintegrating tablet. Online pharmacies charge $15 to $25 per pill for the brand name (Zofran), with little price differential for the generic version at this time. Inpatient and hospital pharmacy charges are often higher, with costs approaching $50 per tablet (Kara M. Bozik, PharmD, BCPS, e-mail communication, March 6, 2007).

We did not undertake a formal cost-benefit or cost-effectiveness analysis. However, given the costs associated with IVF or hospital admission and the relatively low NNTs demonstrated in the present study, ondansetron use in EDs is likely to be cost-effective. For example, based on the summary data, 1 hospital admission, often costing thousands of dollars, can be prevented by treating 14 children with ondansetron at $50 per child, or $700 total. There is probably additional cost benefit to the reduction of IVF use and a cost-utility benefit of short-term vomiting cessation. Formal cost-effectiveness and cost-utility analyses should be performed to confirm these impressions.

Ondansetron is the only antiemetic agent with consistent, proven efficacy in reducing vomiting from gastroenteritis. Other antiemetic drugs have not demonstrated consistent effectiveness and, therefore, should not be used. In addition, moderately ill children presenting to the ED who were treated with ondansetron have a decreased risk of receiving IVF and a decreased need for immediate hospital admission. Ondansetron likely causes a short-term increase in diarrheal episodes without other adverse effects. Although there is currently no evidence that children with mild gastroenteritis benefit from treatment with ondansetron, government agencies and professional societies should strongly consider amending current gastroenteritis treatment guidelines to incorporate the use of ondansetron for certain children with gastroenteritis.

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Author Contributions: Drs DeCamp and Steiner had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: DeCamp, Byerley, and Steiner. Acquisition of data: DeCamp, Byerley, Doshi, and Steiner. Analysis and interpretation of data: DeCamp, Byerley, Doshi, and Steiner. Drafting of the manuscript: DeCamp and Steiner. Critical revision of the manuscript for important intellectual content: DeCamp, Byerley, Doshi, and Steiner. Statistical analysis: DeCamp and Steiner. Administrative, technical, or material support: DeCamp and Steiner. Study supervision: DeCamp and Steiner.

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