Office of Evidence Based Practice (EBP) – Critically Appraised Topic: Use of Antiemetics for Acute Gastroenteritis (AGE)

Specific Care Question

For otherwise healthy patients 2 months to 10 years of age with vomiting and or diarrhea for at least 24 hours should ondansetron be added to therapy in the emergency department (ED) and or urgent care center (UCC) to decrease the need for IV fluid therapy, hospital admission, vomiting, or length of stay?

Recommendations from the Acute Gastroenteritis (AGE) in the ED/UCC Team

A strong recommendation is made for Ondansetron, based on the GRADE evidence to decision instrument. The overall certainty in the evidence is low. Ondansetron has been shown to decrease vomiting in previously healthy patients who present to the ED/UCC with AGE and allows for successful oral rehydration. However, the included trials used different forms of ondansetron and number of doses. Adverse events, such as increase in diarrhea, or changes in QT prolongation are not well reported in the included studies. Per FDA recommendations, baseline EKG should be considered in patients < 4-months of age, with close monitoring for prolonged QT interval. (FDA, 2011; LexiComp, 2019).

Literature Summary

Background. AGE is a common illness among infants and children. Over 10,000 patients with AGE are seen per year in the Children's Mercy EDs and UCCs (Children's Mercy data, May 22, 2018). Oral rehydration and antiemetic therapy are mainstay therapies in the ED/UCC to treat dehydration that ensues from diarrheal illness (Applegate, Fischer Walker, Ambikapathi, & Black, 2013). Ondansetron is used in developed countries to decrease vomiting that often accompanies AGE so that oral rehydration can be successful. However, there are few randomized control trials (RCT) that have been published that support what is reported clinically. There are concerns that ondansetron may increase diarrhea (Freedman et al., 2015), and prolong QT intervals. Adverse events, such as increase in diarrhea or changes in QT prolongation were not well studied, or reported, in the studies identified for this analysis.

Study characteristics. The search for suitable studies was completed on June 11, 2018. JD Nolen, PhD, MD and Jeff Michael, DO reviewed the 95 titles and/or abstracts found in the search and identified 20 articles believed to answer the question. After an in-depth review nine articles answered the question (see Figure 1). There were three systematic reviews with meta-analyses (SR/MA), Das, Kumar, Salam, Freedman, and Bhutta (2013), Freedman, Ali, Oleszczuk, Gouin, and Hartling (2013), and Freedman et al. (2015); three RCTs, Danewa, Shah, Batra, Bhattacharya, and Gupta (2016), Golshekan, Badeli, Rezaieian, Mohammadpour, and Hassanzadehrad (2013), and Hagbom et al. (2017); and three cohort studies: Hendrickson, Zaremba, Wey, Gaillard, and Kharbanda (2018), Mullarkey, Crowley, and Martin (2013), and Rutman, Klein, and Brown (2017).

All three systematic reviews and meta-analyses used strong methods to complete their syntheses. However, the results of the SR/MA could not be combined due to the heterogeneity of results reporting. For example, Das et al. (2013) reported on subjects less than 12 years and reported outcomes in log risk ratios. While, Freedman et al. (2013) and Freedman et al. (2015) reported on subjects less than 18 years and outcomes were reported only as total number of subjects, not number of subjects by treatment received. Therefore, the combined results are reported narratively. All SR/MAs included subjects who were usually healthy.

The three RCTs compared ondansetron to placebo. The risk of bias in the RCTs was moderate, with high risk of attrition bias in two of the three trials (see Figure 2). Danewa et al. (2016) included subjects between 3 months and 5 years of age and treated with ondansetron syrup, Golshekan et al. (2013) recruited subjects between one and 10 years of age and treated with tablets, while Hagbom et al. (2017) included subjects between 6 months and 16 years of age treated with an undetermined medication form.

The cohort studies varied in scope and processes employed. Hendrickson et al. (2018) is a pre-post intervention report where a standardized dehydration scale was employed to trigger a nurse driven protocol in the administration of antiemetics to patients with AGE in an ED triage

area. Mullarkey et al. (2013) was a comparison of retrospective data with post intervention data. Pre-intervention practice was to start IV fluids if a patient with AGE vomited or refused ORT. The post-intervention was to treat the patients who vomited or refused ORT with oral ondansetron and treat with ORT 30 minutes after medication administration. Finally, Rutman et al. (2017) was a quality improvement project where a clinical standard work pathway was employed that focused on providing ORT and using ondansetron to decrease vomiting.

Summary by Outcome

Oral Rehydration Failure. Two RCTs (*n* = 343) measured oral rehydration failure (Danewa et al., 2016; Golshekan et al., 2013). The odds ratio indicated significantly fewer occurrences of oral rehydration failure for subjects who received ondansetron, reported as number of subjects who required IV hydration therapy, *OR* = 0.33, 95% CI [0.2, 0.54]. They are included in the meta-analysis, (see Figure 3 & Table 1). The certainty of the evidence is low based on serious inconsistency and imprecision. Trials were inconsistent because the age of included subjects varied across studies, the form of the medication administered, and the number of doses provided. The findings are imprecise because total number of subjects in each meta-analysis is low.

Previous systematic reviews/meta-analyses report decreased risk of IV hydration when treated with ondansetron. Das et al. (2013) did not report the number of included subjects. Das et al. (2013) reported decreased risk in the group treated with ondansetron, *RR* = 0.4, 95% CI [0.29, 0.56]; as did Freedman et al. (2013), *RR* = 0.41, 95% CI [0.29, 0.59]; and Freedman et al. (2015), *RR* = 0.4, 95% CI [0.26, 0.60]. The certainty of the evidence is low based on serious inconsistency and imprecision. Trials were inconsistent as the ages of subjects varied across studies, and the number of doses varied.

The three cohort studies included in the analysis measured oral rehydration failure (Hendrickson et al., 2018; Mullarkey et al., 2013; Rutman et al., 2017). All three cohorts are comparisons of IV rehydration therapy before and after an intervention to manage care of previously healthy subjects who presented to the ED with AGE. A nurse driven protocol to administer anti-emetics in ED triage (*n* = 128) reported a decrease in IV rehydration from 23% pre-intervention to 9% post-intervention (Hendrickson et al., 2018). A parent education sheet was provided in the ED (*n* = 491) and there was a decrease in IV rehydration from 40.9% pre-intervention to 21.79% post-intervention (Mullarkey et al., 2013). Finally, a clinical standard work process (n = 30,519) for the management of children with AGE was employed and reported a decrease in IV rehydration from 48% pre-intervention to 44% post-intervention (Rutman et al., 2017). The standard work included a clinical pathway and altering location of ondansetron in the automated dispensing cabinet. The evidence was of low-quality based study design. Although each of the cohort studies used a unique intervention, the estimate of effect was large, and supported the evidence presented in the RCTs and systematic reviews/meta-analyses.

Vomiting episodes within 24 hours of treatment. Two RCTs (*n* = 248) measured vomiting episodes within 24 hours of treatment (Danewa et al., 2016; Hagbom et al., 2017). These RCTs reported vomiting within 24 hours of treatment as mean difference, whereas Golshekan et al. (2013) reported differences in counts of vomiting within four hours of treatment (*n* = 176) and is reported as an odds ratio. From the studies that reported vomiting with 24 hours of treatment, vomiting was less in the group treated with ondansetron, *MD* = -1.05, 95% CI [-1.63, -0.47] (Danewa et al., 2016; Hagbom et al., 2017) (see Figure 4). Golsheken et al. (2013) reported no difference in vomiting within four hours of treatment, *OR* = 0.68, 95% CI [0.28, 1.62].

Das et al. (2013) is a SR/MA that reported on four trials that measured vomiting as an outcome. The reporting of results was dissimilar among the included studies, and information such as number of subjects in each group were missing from the SR/MA. Also, the studies differed on the number of hours subjects were assessed for vomiting. However, after treatment with ondansetron, vomiting was less than those subjects treated with placebo *RR* = 0.35, 95% CI [0.26, 0.46].

Identification of Studies

Search Strategy and Results (see Figure 1)

Search: ("Gastroenteritis"[Mesh] OR "gastroenteritis"[tw] OR "diarrhea"[tw] OR "diarrhoea"[tw]) AND ("Probiotics"[Mesh] OR probiotic*[tw]) AND (infant OR pediatr* OR child OR children OR childhood OR paediatr*) AND (("2013/01/01"[PDat]: "2018/12/31"[PDat])) Filters: Meta-Analysis, Systematic Reviews

Records identified through database searching *n* = 95

Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
Danewa et al. (2016)	RCT
Das et al. (2013)	Systematic review
Freedman et al. (2013)	Systematic review
Freedman et al. (2015)	Systematic review
Golshekan et al. (2013)	RCT
Hagbom et al. (2017)	RCT
Hendrickson et al. (2018)	Cohort study
Mullarkey et al. (2013)	Cohort study
Rutman et al. (2017)	Quality study

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Carson, Mudd, and Madati (2016)	Used for background information
Epifanio et al. (2018)	Does not answer the question
S. B. Freedman, DeGroot, and Parkin (2014)	Does not answer the question- asks if bicarbonate levels predict successful discharge
Guarino et al. (2014)	Does not discuss antiemetic therapy
Kita et al. (2015)	Does not answer the question -compares to medicine not available in the US
Marchetti et al. (2016)	Does not answer the question -compares to medicine not available in the US
Pieścik-Lech, Shamir, Guarino, and Szajewska (2013)	Does not answer the question
Rerksuppaphol and Rerksuppaphol (2013)	Does not answer the question -compares to medicine not available in the US
Thompson et al. (2016)	Very high risk of bias across all domains
Tomasik, Ziółkowska, Kołodziej, and Szajewska (2016)	Systematic review that includes studies excluded by our team.

Methods Used for Appraisal and Synthesis

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.
[d]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table(s) for this analysis (see Table 1).
[e]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. Systematic Reviews, 5(1), 210. doi:10.1186/s13643-016-0384-4
[c]Higgins, J. P. T., & Green, S. e. (2011). Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011] (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.
[d]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.
[e]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit www.prisma-statement.org.

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Acronyms Used in this Document

Acronym	Explanation
AGE	Acute gastroenteritis
CHERG	Child Health Epidemiology Reference Group
CPG	Clinical Practice Guideline
EBP	Evidence Based Practice
ED	Emergency Department
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
MeSH	Medical Subject Headings
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Control Trial
RoB	Risk of Bias

UCC	Urgent Care Center
WHO	World Health Organization

Date Developed
February 2019

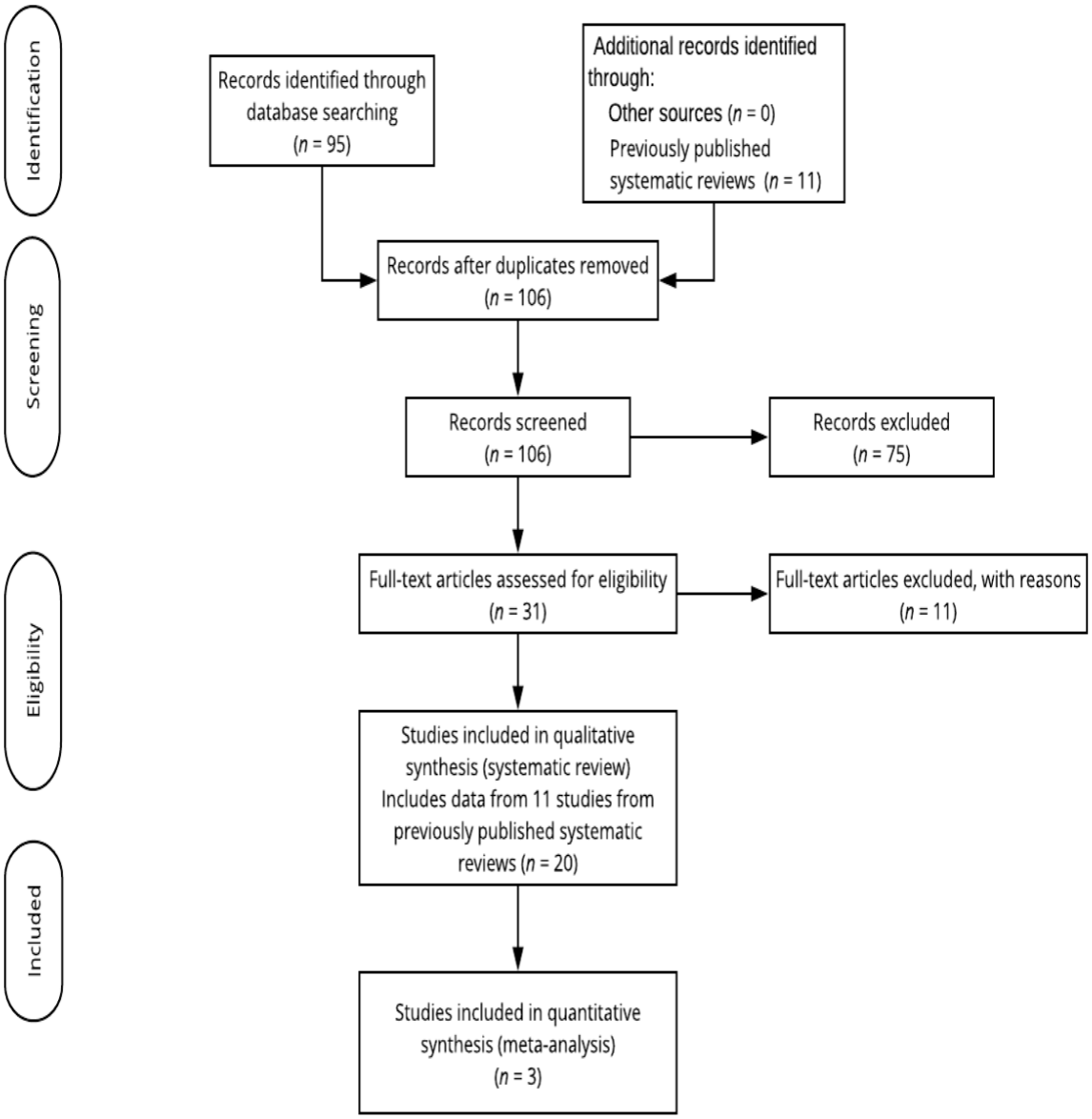

Figure 1. **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]**

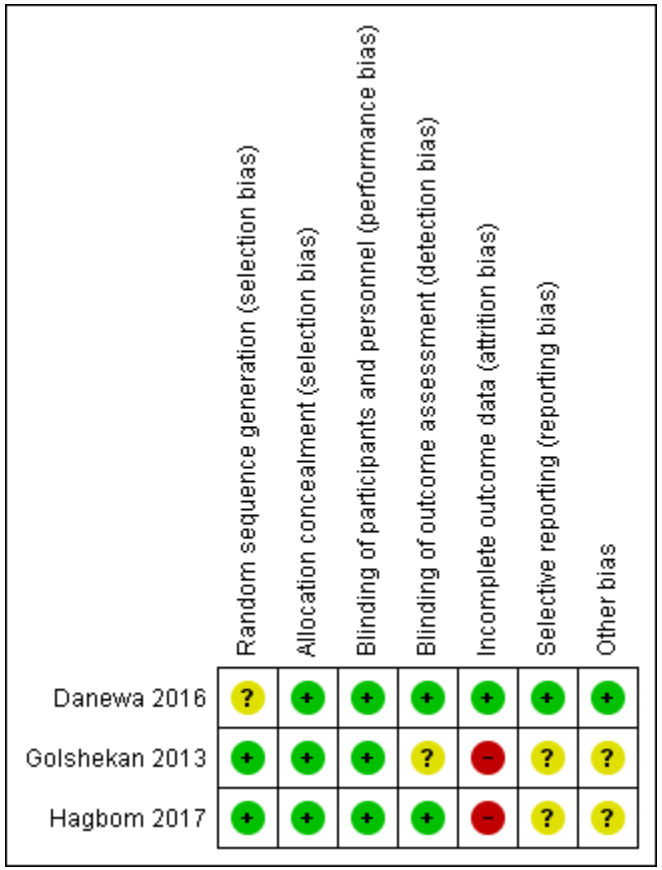

Figure 2. **Risk of Bias Summary**

Table 1

Summary of Findings Table: Ondansetron Compared to Placebo for Acute Gastroenteritis

Certainty assessment							Summary of findings				
Nº of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With ondansetron		Risk with placebo	Risk difference with ondansetron
Vomiting episodes within 24 hours of treatment											
248 (2 RCTs)	serious [a]	serious [b]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	-	-	***MD* = -1.05** (-1.63 to 0.47)	The mean vomiting episodes within 24 hours of treatment was **2**.27	*MD* **1.05 lower** (1.63 lower to 0.47 lower)
Oral rehydration failure											
343 (2 RCTs)	serious [a]	not serious	serious [d]	very serious [e]	none	⨁◯◯◯ VERY LOW	75/171 (43.9%)	38/172 (22.1%)	**OR 0.33** (0.20 to 0.54)	439 per 1,000	**234 fewer per 1,000** (303 fewer to 142 fewer)
Oral re-hydration failure (observational studies)											
31143 (3 observational studies)	serious [f]	serious [g]	not serious	not serious	none	⨁⨁◯◯ LOW	2089/4409 (47.4%)	11661/26734 (43.6%)	**OR 0.83** (0.78 to 0.89)	474 per 1,000	**46 fewer per 1,000** (61 fewer to 29 fewer)

Notes:

a. Both studies used per protocol analysis. In one of the studies, only two sub-groups were used in the analysis, evidence of selective reporting bias.

b. The results of the two included studies are not consistent. One study reports a significant difference, a decrease of approximately 2 vomiting episodes in the 24 hours after treatment. However, the other study reported no difference in the number of vomiting episodes. The I_2 statistic is a measure statistical heterogeneity. The desired I_2 is < 50% and the I2 statistic for this outcome is 90%.

c. There are only two studies, with a total of 248 included subjects. Certainty in the precision of the findings is surer when there are greater number of subjects.

d. One of the studies had low risk of bias across all domains. However, the other trial did not clearly report the blinding of the outcome assessors, and the denominator changes throughout the analysis. The analysis is broken into age ranges, weight ranges, or sex for each outcome, with no total reporting available.
e. There are only two studies, with a total of 243 included subjects. Certainty in the precision of the findings is surer when there are greater number of subjects.
f. All 3 trials are pre-post cohort studies.
g. The interventions they used varied among the trials, one instantiated a nursing standing order, one engaged in formalized parent education, and one created standard clinical work to affect the care of patients with AGE. I_2 = 90%

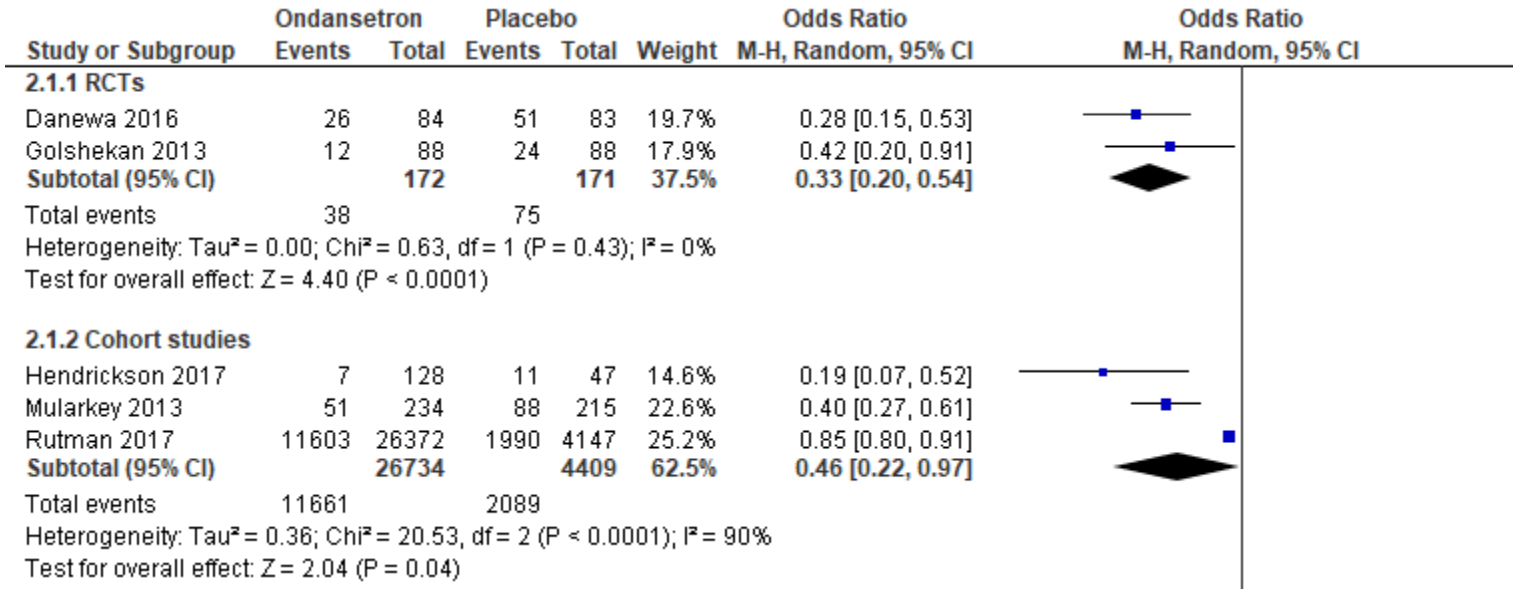

Figure 3. **Comparison: Ondansetron versus Placebo, Outcome: Oral rehydration failure, IV hydration started**

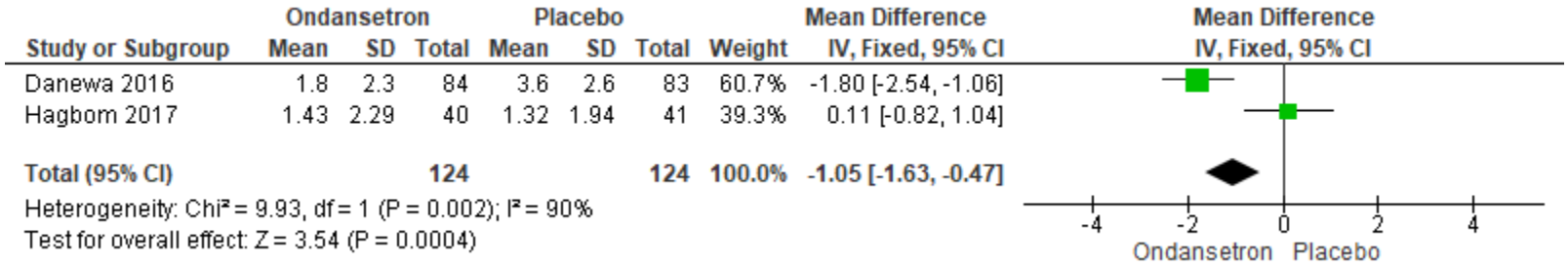

Figure 4. **Comparison: Ondansetron versus Placebo, Outcome: Vomiting episodes within 24 hours of treatment**

Characteristics of Studies

Danewa 2016

Methods	RCT

Participants	**Setting:** Pediatric emergency unit, Delhi, India
	Randomized into study: *N* = 170
	• **Ondansetron, syrup:** *n* = 85
	• **Group 2:** *n* = 85
	Completed Study: *N* = 167
	• **Ondansetron, syrup:** *n* = 84
	• **Placebo:** *n* = 83
	Gender, males:
	• **Ondansetron, syrup:** *n* = 54 (63.5%)
	• **Placebo:** *n* = 45 (52.9%)
	Age, months (mean) (SD):
	• **Ondansetron, syrup:** 15.5 (10.7)
	• **Placebo:** 15.0 (9.5)
	Inclusion Criteria:
	• Between 3-months and 5 years of age
	• Acute diarrhea, defined as less than 14 days
	• Some dehydration by World Health Organization (WHO) criteria
	• At least 2 reported episodes of non-bloody, non-bilious vomiting within the previous 6-hours
	Exclusion Criteria:
	• Patients with severe malnutrition (less than 3 standard deviations below WHO Standards
	• Presence of
	  ○ Edema
	  ○ Unconsciousness
	  ○ Convulsions
	  ○ Paralytic ileus (presence of abdominal distension, not passing stool, and diminished or absent bowel sounds
	• Patients who had taken an antiemetic within the previous 24-hours
	• Patients who had received intravenous fluids for this diarrhea illness
	Power Analysis: Yes, based on external (Freedman, 2006) and internal data, it was calculated to reduce the IV fluid use by 20% with 90% power and an alpha of .05, 82 subjects were required in each group.

Interventions	**Both:** Medication was prepared into a syringe. Study personnel transferred the medication to a spoon and administered it to the subject. The same dose of medication was repeated once if the subject vomited with 30 minutes of administration. After taking the medication, subjects in both groups were given WHO ORS at 75 ml/kg within the first 4-hours. WHO ORS continued for subjects who still had signs /symptoms of dehydration. Subjects with signs of severe dehydration or shock were treated with IV fluids. Infants were encouraged to breastfeed through treatment. All subjects remained for 2-hours after the correction of dehydration. Oral zinc

	was provided for all subjects for 14 days, 10 mg/day for 3 to 6-months old and 20 mg/d in two divided doses for subjects greater than 6-months of age. • **Ondansetron, syrup:** Ondansetron syrup (2 mg/5 ml) • **Placebo:** Placebo
Outcomes	**Primary outcome(s):** • Failure of ORT • Administration of unscheduled IF fluid • Amount of ORS intake in 4-hours **Secondary outcome(s)** • Duration of dehydration correction • Number of vomiting episodes in 4 - hours • Caregiver satisfaction ·**Safety outcome(s):** • Adverse effects such as rash, headache, diarrhea

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Unclear risk	Computer generated block randomization
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Medications were prepared by person not involved in the study. Medications were made of similar composition, except the active medication
Blinding of outcome assessment (detection bias)	Low risk	All were blinded to allocation, and medication type
Incomplete outcome data (attrition bias)	Low risk	Few drop-outs (3) for same reasons in each group. Sensitivity analysis with drop-outs added back in, did not change the results.
Selective reporting (reporting bias)	Low risk	Reported on all intended variables
Other bias	Low risk	

Das, 2013

Design	Quantitative Synthesis (meta-analysis)
Objective	In children 0 – 12 years with AGE, do antiemetics reduce the incidence of vomiting, hospitalization, revisits, and IV rehydration requirement?
Methods	**Protocol and registration.** The protocol was not registered. **Eligibility Criteria.** • Randomized and quasi-randomized trial where any antiemetic was administered to children with vomiting associated with AGE • Any dose of antiemetic administered orally, intravenously, suppository • Age 0-12 years • Excluded: studies on adults, vomiting due to non-AGE, no placebo/control group **Information sources. All published literature until January 2012** • PubMed • Medline • Cochrane Libraries • EMBASE • World Health Organization (WHO) **Search.** • Medical Subject Heading Terms (MeSH) • Keyword search strategy using various combinations of gastroenteritis, vomiting, antiemetics, children • No language or date restrictions in the electronic search **Study Selection.** • Search results were screened independently by two reviewers to identify potentially relevant citations. • The full text of potentially relevant citations was assessed for inclusion by two independent reviewers using predefined criteria. • Disagreements were resolved by consensus. **Data collection process.** • Each study was assessed and graded according to the Child Health Epidemiology Reference Group (CHERG) adaptation of the GRADE technique. • Individual studies were graded according to strengths and limitations of study. • A study was downgraded if there were limitations in the conduct of the study. • A grade of "high", "moderate", "low" and "very low" was used for grading the overall evidence indicating the strength of an effect on specific health outcome.

Risk of bias (RoB) across studies.

Risk of bias in the included studies was assessed according to the latest Cochrane Handbook.

Summary measures.

Risk Ratio (RR) was reported for the following outcomes:

- Vomiting
- Hospitalization
- Revisit rate
- IVF requirement rate
- ORT tolerance rate

Synthesis of results.

- Vomiting (used random effect model due to heterogeneity being high)
- Hospitalization (used fixed effect model due to heterogeneity being low)
- Revisit rate (used fixed effect model due to no significant heterogeneity)
- IVF requirement rate (used fixed effect model due to heterogeneity being low)
- ORT tolerance rate (no mention of model used, RR listed for different antiemetics)

Additional analyses.

Subgroup analyses were done for different antiemetics. No plan for meta regression.

Results

Study Selection.

Number of articles identified: *N* = 910

- **Full-text articles assessed for eligibility:** *n* = 20
- **Studies included in quantitative synthesis:** *n* = 7

Synthesis of results.

Quality Assessment of trials of antiemetics:

Comparison Outcome	Number of studies	Total subjects	Relative Risk *RR* [95% CI]
Vomiting			
Pooled different emetics	6	305	.46 [.35, .61]
Oral Ondansetron	4	181	0.35 [0.26, 0.46]
IV ondansetron	1	15	0.5 [0.24, 1.04]
IV metoclopramide	1	18	0.8 [0.50, 1.28]
Rectal dimenhydrinate	1	91	0.6 [0.44, 0.82]
Hospitalization rate			
Pooled different antiemetics	6	80	0.46 [.029, 0.74]
Oral Ondansetron	4	44	0.36 [0.18, 0.72]

IV ondansetron	1	11	0.21 [0.05, 0.94]
IV metoclopramide	1	16	0.73 [0.30, 1.79]
Rectal dimenhydrinate	1	9	0.77 [0.21, 2.78]
Revisit rate			
Oral ondansetron	4	unclear	0.97 [0.62, 1.53]
IV rehydration required			
IVF required	3	128	0.4 [0.29, 0.56]

Results of Forest Plots summary:

Comparison Outcome	Weight, %	Risk Ratio *RR* [95% CI]	Heterogeneity
Vomiting			
Rectal Dimenhydrinate	22.0	0.6 [0.44, 0.82]	
IV ondansetron	9.7	0.5 [0.24, 1.04]	
Oral ondansetron	52.1	0.35 [0.26,0.46]	I_2 = 0%
IV metoclopramide	16.2	0.8 [0.50, 1.28]	
Total vomiting	100	0.46 [0.35, 0.61]	I_2 = 73.3%
Hospitalization			
Oral ondansetron	47.9	0.36 [0.18, 0.72]	I_2 = 7%
IV ondansetron	10.4	0.21 [0.05, 0.94]	
Rectal dimenhydrinate	13.7	0.77 [0.21, 2.78]	
IV dexamethasone	28.0	0.8 [0.50, 1.28]	
Total hospitalization	100	0.73 [0.3, 1.79]	I_2 = 3.8%

Risk of bias across studies. Unable to asses RoB from the manner of reporting. It appears that risk of bias in the methods of individual studies, and the quality of evidence of pooled studies is combined. Bias is not specifically reported.

	Additional analysis. If there was inconsistency among the studies, random effects model was used, otherwise a fixed effect model was employed.
Discussion	**Summary of evidence.** **Outcome: Vomiting** Antiemetics were associated with a 54% reduction in the incidence of vomiting **Outcome: Hospitalization** 54% reduction in the incidence of hospitalization after the use of antiemetics **Outcome: Revisit rate** Oral ondansetron reduced the revisit rate to the ED by 3% **Outcome: IVF rate** • Oral ondansetron reduced IVF requirements during ED stay by 60% • Oral ondansetron reduced IVF requirements within 72 hours of discharge by 34% **Limitations.** • Study only done for ED setting, further study needed for primary care setting • Study not specific to 0-5 years, which was the original intent of study
Funding	**Funding.** Publication costs covered by grant, authors state that they have no competing interests.

Freedman, 2013

Design	**Quantitative Synthesis (meta-analysis)**
Objective	To evaluate the evidence regarding the efficacy and safety of commonly considered treatment options in children with AGE in the Cochrane Database of Systematic Reviews. **P:** Children with AGE **Intervention** / **Comparison** Oral rehydration (ORT) / Intravenous (IV) rehydration Oral ondansetron / Placebo IV ondansetron / Placebo Probiotic / No probiotic **Outcome(s).** • Rate of admission to the hospital * • Length of stay in hospital (LOS) * • Rate of return visits * • Administration of IV therapy due to failure of ORT * • Adverse events • Dysnatremia

Methods	**Protocol and registration.** Information not reported **Eligibility Criteria.** Children under 18 years of age with AGE and potential eligibility for ORT, anti-emetics and probiotics **Information sources.** • Medline (1946 to present) • Cochran Database of Systematic Reviews (2005 to November 2011) • Embase (1980 to present) • Global Health (1910 to March 2012) • PubMed (October 2011 to May 2012) **Search.** • Study only intended to include reviews of RCT trials published in the CDRS. • Expanded to include a non-Cochrane review. **Study Selection.** • Two reviewers independently screened the results of the literature research • Full texts of potentially relevant articles were retrieved, independently screened and assessed for inclusion • Disagreements were resolved through discussion **Data collection process.** • One reviewer extracted search methods, inclusion criteria, methodological quality of the included trials and numerical results • Second reviewer independently verified extracted data **Risk of bias (RoB) across studies.** • Cochrane risk of bias tool used for two Cochrane study. • No description of risk of bias for two studies **Summary measures.** • For continuous data, mean differences (MD) with 95% confidence interval (CI) • For dichotomous data, risk ratios (RR) with 95% CI were used in two reviews, owing to frequent zero event rates, risk difference (RD) rather than RR were used in one review. • To quantify the degree of the treatment effect for dichotomous outcomes that were statistically significant, we calculated the number needed to treat (NNT). **Synthesis of results.** • Review Manager 5 was used to conduct additional analyses that were not included in the original reviews

Study Selection.

Number of articles identified: *N* = 3,419

- **Systematic reviews identified:** *n* = 4
- **Studies included in quantitative synthesis:** *n* = 95

Synthesis of results.

Outcome	Number of Studies	Number of subjects	Results (*RR, OR, MD*) [95% CI]	I_2
ORT versus IV therapy				
Length of stay	6	526	*MD* = -1.20 (-2.38 to -.02)	95%
Outlier removed	5	326	*MD* = -.34 (-.77 to.08)	55%
IV ondansetron versus placebo				
Hospitalization	1	90	*RR* = .21 (.05 to .93)	NA
Oral ondansetron versus placebo				
Hospitalization	3	465	*RR* = .40 (.19 to .83)	17%
Return with hospitalization				
IV Rehydration Best-worst case scenario	3	461	*RR* = .60 (.34 to 1.04)	49%
IV Rehydration Worst-best case scenario	3	461	*RR* = .73 (.43 to 1.22)	0%
Probiotics versus placebo				
Length of stay	10	</= 1932	*MD* = -1.12 (-1.16 to -.38)	Not calculated

Risk of bias across studies.

- Risk of bias was reported for only two of four reviews
- Sequence Generation – High risk for 7 out of 62 studies
- Allocation concealment – High risk for 7 out of 62 studies
- Blinding – High risk for 12 out of 62 studies
- Incomplete outcome data – High risk for 13 out of 62 studies
- Selective reporting – High risk for 0 out of 7 studies
- Other sources of bias – High risk for 4 out of 7 studies.

Discussion

Summary of evidence.

- Children receiving ORT spent less time in the hospital compared to those who received IV rehydration.

	• Children receiving oral or IV ondansetron had unclear rates of admission to the hospital versus placebo. • Probiotic use versus placebo had unclear results on shortening of hospitalization. **Limitations.** • In reference to ORT vs IV rehydration, the review revealed small sample sizes, low quality evidence and the risk for bias was unclear. • The Cochrane review had not been updated since 2006. • In reference to anti-emetics, though the studies were recent and of good quality, they did not fully address clinically significant outcomes.
Funding	**Funding.** Not reported

Freedman 2017

Design	**Quantitative Synthesis (meta-analysis)**
Objective of SR	To examine interventions commonly used in developed countries to treat gastroenteritis. P: For the patient who presents to the ED with acute gastroenteritis **Intervention** / **Comparison** Oral rehydration / IV rehydration Antiemetics / No antiemetics Probiotics / No probiotics Outcomes: Hospitalization, ED return visits, ORT failure, Length of stay, duration of diarrhea
Methods	**Protocol and registration:** The protocol was not registered. A protocol was established and published in supplementary information. **Eligibility Criteria:** • MEDLINE (2000 to April 2012), • EMBASE (2000 to April 2012), • Cochrane Database of Systematic Reviews (2005 to April 2012) via the OvidSP platform; • Appropriate journals and major, relevant scientific meetings; • Reference lists of relevant reviews; • Primary authors were contacted. • The search was not restricted by language or publication status. **Search:** Strategies are in the supplemental information, not in the paper.

Study Selection: State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). May be in the protocol.

Data collection process: They used a two-person review technique, one author extracted the identified factors, and a second author verified the work. If there was conflict, a third author reviewed the work.

Risk of Bias across studies: The Cochrane Risk of Bias tool was used to assess bias by two reviewers, independently. Either consensus between the two reviewers, or a third reviewer was employed to resolve conflicts.

Summary measures: Mean differences were used for continuous variables, using a weighted mean difference and inverse-variance methods. For dichotomous outcomes, risk ratios or risk differences were reported.

Synthesis of results: Confidence intervals are at 95% CI, and random effect models were utilized. If sensitivity analysis was performed, a fixed effects model was utilized. RevMan 5.0 was used for analysis.

Additional analyses: If heterogeneity was > 75% the data was not pooled. Unable to perform test for publication bias, as there were an insufficient number of included studies.

Results

Study Selection Give numbers of studies screened, assessed for eligibility, and included in the review.

Number of articles identified: *N* = 10,353

- **Full-text articles assessed for eligibility:** *n* = 475
- **Studies included in qualitative synthesis:** *n* = 31
- **Studies included in quantitative synthesis:** *n* = 31

Synthesis of results:

Comparison Outcome	Number of studies	Total subjects	Risk ratio *RR* [95% CI]	I_2
ORT				
Hospitalization	3	136	.8 [0.24, 2.71]	51%
Return to ED	3	193	.86 [0.39, 1.89]	0%
Antiemetic therapy				
Hospitalization	7	1043	.44 [.23, .82]	27%
Return to ED	8	1074	1.31 [0.73, 2.35]	52%
ORT failure	5	733	.4 [.26, .60]	30%
Probiotics				
Hospitalization	3	833	.53 [0.26, 1.07]	20%
Return to ED	1	23	.78 [0.36, 1.67]	N/A
ORT Failure	1	44	1.13 [0.81, 1.57]	N/A

	Risk of bias across studies: For 23% (7/31) of the trials risk of bias was low unclear for 74% (23/31), and high for 3% (1/31). Industry funding was recognized in 50% (5/10) of the antiemetic studies, 38% (3/8) of probiotic studies, and 33% (2/6) of the need for ORT failure studies. **Additional analysis:** There is a comparison of composition of intravenous fluids and speed of intravenous fluid administration, however this comparison does not answer the question being asked and is not included.
Discussion	**Summary of evidence**: ORT is an effective intervention. It is low cost and non-invasive. Use of probiotics cannot be recommended from this analysis, continuing research is likely to change the recommendation. Although ondansetron may increase the frequency of diarrhea, its role in reducing vomiting of ORT, is a factor in successful ORT. In this analysis, it decreased the need for intravenous fluid administration and hospitalization. **Limitations**: The included studies only included outpatients, and the results may not apply to patients who are at home, nor hospitalized patients. The planned subgroup analysis could not be performed due to the inability to create the groups, as reporting ranges varied.
Funding	**Funding:** This study was funded by the Canadian Institutes of Health Research. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Golshekan 2013

Methods	RCT
Participants	**Setting:** Emergency Department, Children's Hospital in Rasht, Iran **Randomized into study:** *N* = 176 • **Group 1,** Ondansetron: *n* = 88 • **Group 2:** Placebo, *n* = 88 **Completed Study:** *N* = 165 • **Group 1,** Ondansetron**:** *n* = 82 • **Group 2:** Placebo, *n* = 83 **Gender, males:** 58.5% **Age, months/years** mean (SD): 2.3 (3.12) **Inclusion Criteria:** • Between 1 and 10 years of age • Simple acute gastroenteritis, • Dehydration • Onset in the previous 24 hours • At least one vomiting episode in the previous 6 hours • No fever, or low fever < 38.2 degrees Celsius **Exclusion Criteria:** • Any antiemetic medication in the last 24 hours

	• Any chronic disease • Alarming signs of dehydration or shock • More than one diarrhea episode in one hour • Does not tolerate 5HT3 receptor inhibitor medication **Power Analysis:** Not reported
Interventions	• · **Both:** Dosing was weight based ○ Subjects < 15-kilogram 1/2 tablet - 2 milligrams ○ Subjects between 15 and 30-kilogram 1 tablet - 4 milligrams ○ Subjects > 30 kilograms - 1.5 tablets- 6 milligram • **Group 1:** Weight based dose, dissolved in 2 cc of water • **Group 2:** Weight based number of placebo tablets, dissolved in 2 cc of water
Outcomes	**Primary outcome(s):** • Vomiting during 4 hours of ORT • Vomiting during 48 hours after discharge ·**Secondary outcome(s):** • Need IV rehydration • Need hospitalization

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Computer randomization in blocks of two
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Investigators blinded until after statistical analysis complete
Blinding of outcome assessment (detection bias)	Unclear risk	Not well described
Incomplete outcome data (attrition bias)	High risk	The denominator changes throughout the analysis, Also, the analysis is broken into age ranges, weight ranges, or sex for each outcome they report upon.
Selective reporting (reporting bias)	Unclear risk	
Other bias	Unclear risk	

Hagbom 2017

Methods	Randomized double-blinded placebo-controlled trial

Participants	**Setting:** Queen Silvia Children's Hospital Gothenburg, Sweden
	Randomized into study: *N* = 104
	Completed study for primary outcome: *N* = 101
	Completed study for secondary outcome: *N* = 79
	Included in outcome analysis: *N* = 82
	• Rotavirus (RV) or norovirus (noV) infection positive
	• **Group1:** *n* = 40
	  ○ Ondansetron
	• **Group 2:** *n* = 41
	  ○ Placebo
	Gender, males:
	• **Group1:** 19 (46%)
	• **Group 2:** 18 (44%)
	Age, months mean (SD):
	Group1: 28.70 ± 18.38
	Group 2: 28.22 ± 22.99
	Inclusion criteria:
	• Children aged 6 months to 16 years
	• At least one episode of vomiting during the last four hours
	• At least one episode on non-bloody diarrhea during sickness period
	Exclusion criteria:
	• Severe dehydration
	• Allergy to ondansetron
	• Previous abdominal surgery
	• Use of antiemetics during last 72 hours
	• Previous participation in the study
	• Severe congenital heart defects
	• Immune deficiency
	• Malignancy
	• Malnutrition
	• Cystic fibrosis
	• Sickle cell anemia
	• Fructose intolerance
	• Diabetes mellitus
	• Suspected other diseases than gastroenteritis
	Power Analysis:

	• Our assumption was that approximately 60% of the children with AGE would be suffering from a RV- or NoV-infection, a calculation based on previous etiology studies [4, 27±30]. We estimated the proportion of RV or NoV children who vomited after treatment to be50% in the control group and 20% in the treatment group. Based on this we calculated that enrollment of 133 children (corresponding to 80 RV or NoV positives) would yield a power of 80%, with two-sided significance level of 95%. Due to difficulties in recruiting children, we reached a number of 104 participants during the two-year study period. However, the proportion of children with AGE due to RV and NoV was higher than expected, with 86 children being RV or NoV positive.
Interventions	**Both Groups:** • Examined by physician • If vomiting within 15 minutes of administration of study medication, a second dose was given • Rehydration with oral rehydration solution (ORS) was initiated 15 minutes after study medication • ORS lasted for at least one hour **Intervention:** Ondansetron (0.8mg/ml given in the dose of 0.15mg/kg), oral **Control:** Placebo
Outcomes	**Primary Outcome:** • Number of vomiting and diarrhea episodes within 24 hours of treatment **Secondary Outcome (**Added after the 21st subject**):** • Number of days of diarrhea and or vomiting after treatment

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Random allocation made in blocks (*n* = 8)
Allocation concealment (selection bias)	Low risk	The code key was sealed and stored in a locked cabinet.
Blinding of participants and personnel (performance bias)	Low risk	Drug and placebo were labeled-blinded with A or B with identical taste, odor, color and volume
Blinding of outcome assessment (detection bias)	Low risk	Blinded member of study team made phone calls for outcomes
Incomplete outcome data (attrition bias)	High risk	Per protocol analysis. They randomized 104 subjects, but only included those with rotavirus or norovirus infection in the analysis, *n* = 81 for the primary outcome and n = 64 for the secondary outcome.
Selective reporting (reporting bias)	Unclear risk	All pre-specified primary and secondary outcomes have been reported, However, they added the secondary outcome after 21 subjects were entered into the protocol.

Other bias	Unclear risk	

Hendrickson 2017

Methods	Prospective post-intervention data compared with retrospective, pre-intervention subjects in children aged 6 months to 5 years with symptoms of acute gastroenteritis to assess the implementation of a nurse driven protocol to administer anti-emetics to patients with AGE in ED triage.
Participants	**Participants:** Children age 6 months to 5 years with acute diarrhea with or without vomiting **Setting:** Pediatric emergency department, U.S.A. **Number enrolled:** *N* = 128 • Pre: *n* = 41 • Post: *n* = 81 **Number completed:** *N* = 128 **Gender, males:** • Pre: *n* = 30 (64%) • Post: *n* = 53 (65%) **Age, years:** • Pre: *n* = 1.9 (1.2) • Post: *n* = 2.2 (1.3) **Inclusion Criteria:** • 6 months-5 years • Diarrhea with or without vomiting **Exclusion Criteria:** • Relevant chronic disease • Vomiting without diarrhea • Severe abdominal pain **Covariates identified:** Abdominal pain and vomiting

Interventions	• **Pre-intervention**: Review of fluids offered and consumed by participants
	• **Post-intervention**: Degree of dehydration using standardized scale,
	  ○ "No" dehydration (score 0-1) unstructured oral challenge
	  ○ "Some" (score 2-4) formal oral rehydration therapy (ORT) administered
	  ○ "Moderate or severe" dehydration no triage intervention administered.
	• Regardless of degree of dehydration, active or recent vomiting participants administered ondansetron prior to oral challenge or ORT

Outcomes	**Primary outcome(s):** • Use of ORT* • Use of anti-emetics* • IVF utilization* **Secondary outcome(s):**

	• Admission rate • Unscheduled return for persistent symptoms • Laboratory testing* • ED length of stay • Documentation ORT* *Outcome requested by CPG team
Notes	**Results:** • Pre: *n* = 47 • Post: *n* = 81 Ondansetron use: *p* < .001 • Pre: 17 (36%) • Post: 61 (75%) Documentation of ORT: *p* < .001 • Pre: 24 (51%) • Post: 77 (100%) Time to ondansetron in minutes, Mean (SD): *p* = .004 • Pre: 60 (36.8) • Post: 30 (19.6) Laboratory testing: *p* = .098 • Pre: 17 (37%) • Post: 18 (22%) IVF utilization *p* = .034 • Pre: 11 (23%) • Post: 7 (9%)

Mullarkey 2013

Methods	Cohort Study, postintervention compared with retrospective data
Participants	**Participants**: Children weighing more than 5 kg up to age 16 years old with acute gastroenteritis and poor oral intake **Setting:** Pediatric emergency department, Ireland, October 2009 six-week post intervention compared to six weeks from 2008. **Number enrolled:** *N* = 491 • Study group: *n* = 245 • Comparison group: *n* = 246 **Number completed:** *N* = 449 • Study: *n* = 234 • Comparison: *n* = 215 **Gender, males:**

	• Study: *n* = 120 (51.2%) • Comparison: *n* = 104 (47.3%) **Age, years (mean):** • Study: *n* = 3.40 • Comparison: *n* = 3.27 **Inclusion Criteria**: • Weight >5 kg • Up to 16 years old • Presumptive diagnosis of acute gastroenteritis without other suggestive illnesses • Discharge diagnosis of gastroenteritis **Exclusion Criteria:** • Severe dehydration • Change in consciousness • Severe abdominal pain • Clinical notes documented alternate diagnosis • Hypoglycemia secondary to gastroenteritis **Covariates identified:** • Children that returned to ED within 7 days with ongoing symptoms were included in study endpoint analysis but excluded from analysis of baseline patient characteristics
Interventions	**Study:** • Parents were given information sheet and electrolyte fluid to give to patients. • If child vomited or refused oral rehydration therapy (ORT) child was given a single dose of ondansetron based on weight. Re-dosed if vomiting occurred within 30 minutes of administration of medication. • ORT was restarted 30 minutes after oral medication was administered. If ORT with ondansetron failed child was treated with IVF. **Comparison:** • Parents were given information sheet and electrolyte fluid to give to patients. • If child vomited or refused ORT they were given intravenous fluids (IVF) following medical assessment.
Outcomes	**Primary outcome(s):** • Number of children requiring IVF* • Admission rates* • Return to ED within seven days for ongoing symptoms
Notes	**Results**: **Percent of children requiring IVF**: *p* <.0001 • Study: 21.79% • Comparison: 40.9%

	Number of admissions: *P* = .62 • Study: 30 (12.82%) • Comparison: 31 (14.41%)

Rutman 2017

Methods	Quality improvement study
Participants	**Participants:** Children aged 3 months to 18 years presenting to pediatric emergency department (ED) with acute gastroenteritis (AGE) from January 2003 through April 2015 **Setting:** Tertiary, university-affiliated, 323-bed pediatric hospital with a dedicated pediatric ED **Number enrolled:** *N* = 30,519 • **Group 1:** Pre-pathway *n* = 4147 • **Group 2:** Post-pathway *n* = 26,372 **Number completed:** *N* = 30,519 **Gender, males:** 52% **Age- mean:** Not reported **Inclusion criteria:** • Children aged 3 months to 18 years • Presenting in ED with AGE defined as having an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code associated with both AGE and vomiting • Eligible for AGE pathway **Exclusion criteria:** • <3 months old • Assigned ICD-9-CM or ICD-10 diagnostic codes associated with bloody diarrhea or comorbid conditions (e.g. medical complexity, renal failure, cardiac disease, neurological disease and sepsis)
Interventions	• Implementation of clinical standard work (CSW) pathway for AGE in January of 2005 that focused on oral rehydration therapy (ORT) and with the additional use of ondansetron in March 2006 • Comparison of pre-pathway data to post-pathway data on several specific outcomes namely length of stay (LOS) in ED, use of intravenous fluids, ED returns within 72 hours
Outcomes	**Primary outcome:** • LOS in ED • Use of IV fluids **Secondary outcome:** • ED returns within 72 hours of discharge for AGE related symptoms
Notes	The use of the AGE CSW pathway resulted in a decrease of ED LOS from 247 minutes to 172 minutes. Additionally, the study found that the use of IV fluids decreased from 48% to 44% with the implementation of the CSW for AGE and then further decreased to 26% after the addition of ondansetron the pathway. Both primary outcomes results were sustained overtime. Use of the pathway did not show an effect on ED returns for AGE symptoms within 72 hours.

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