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Clinical Evaluation of the Efficacy and Safety of Ondansetron in Pediatric Acute Gastroenteritis: A Systematic Review of Clinical Profiles, Healthcare Utilization, and Hospital Outcomes

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Abstract

Acute gastroenteritis (AGE) is a common cause of morbidity in children, and vomiting is often an obstacle to effective oral rehydration therapy (ORT). This systematic review aimed to assess the efficacy and safety of ondansetron in treating AGE in children. PubMed, Embase, Scopus, Cochrane Library, and ClinicalTrials.gov were systematically searched from inception to June 2026. We used Zotero for reference management and duplicate removal and Rayyan for study screening. Risk of bias was assessed using the Cochrane Risk of Bias 2 for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for retrospective cohort studies. Due to methodological diversity across studies, a qualitative narrative synthesis was performed. Eight studies comprising 60,191 participants were included, including five RCTs with 2,397 participants and three retrospective cohort studies with 57,794 participants. Among RCTs, ondansetron consistently reduced vomiting compared with placebo or usual care. In one large randomized trial, ondansetron was associated with fewer vomiting episodes within 48 hours (adjusted rate ratio, 0.76; 95% CI, 0.67-0.87), while another randomized trial reported a lower occurrence of moderate-to-severe disease (5.1% vs. 12.5%; adjusted OR, 0.50; 95% CI, 0.40-0.60). The need for IV fluids was also reduced in randomized evidence, with one trial reporting rates of 14% vs. 31% (RR, 0.46; 95% CI, 0.26-0.79). Observational cohort studies provided less consistent evidence regarding healthcare utilization outcomes. Hospitalization rates were 2.0% vs. 10.0% in one cohort and 6.3% vs. 7.2% in another, while ED revisits varied across studies, including rates of 4.0% vs. 4.8% at 72 hours in one cohort (adjusted OR, 0.82; 95% CI, 0.72-0.95), with nonsignificant differences reported in other studies. Regarding safety, one randomized trial reported similar adverse-event rates between ondansetron and placebo (7.0% vs. 7.1%; OR, 0.99; 95% CI, 0.61-1.61), although repeated dosing was associated with more mild diarrhea (rate ratio, 1.36; 95% CI, 1.03-1.80). Overall, the randomized evidence supports ondansetron as an effective adjunct to ORT for reducing vomiting and IV fluid requirements in children with AGE, while observational evidence regarding hospitalization and ED revisits was inconsistent. Because no quantitative meta-analysis was performed, these estimates represent findings from individual studies rather than pooled effects. Further high-quality multicenter studies using standardized outcomes are needed to clarify the effects of ondansetron on healthcare utilization and longer-term safety.

Categories: Pediatrics, Gastroenterology
Keywords: acute gastroenteritis, hospital outcomes, ondansetron, oral rehydration therapy, pediatrics

Introduction And Background

Acute gastroenteritis (AGE) is a major cause of morbidity and healthcare utilization, resulting in millions of ED presentations and hospitalizations among children worldwide. Although oral rehydration therapy (ORT) and rotavirus vaccination have substantially reduced mortality, vomiting remains a major barrier to successful oral rehydration. It may contribute to dehydration, prolonged ED visits, IV fluid administration, and hospital admission [1,2]. Although most episodes of pediatric AGE are self-limited, severe dehydration and associated complications can become life-threatening. They may result in death, particularly among malnourished children and other vulnerable pediatric populations. Thus, effective control of vomiting and successful oral rehydration are important to prevent progression to severe dehydration and optimize clinical outcomes and healthcare resource use [1,2].

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Ondansetron is a selective 5-hydroxytryptamine-3 (5-HT3) receptor antagonist that was initially developed as an antiemetic for chemotherapy-induced nausea and vomiting and has subsequently been increasingly used to manage vomiting associated with pediatric AGE. Ondansetron is generally used as an adjunct to standard supportive management and oral rehydration rather than as a replacement for rehydration therapy. It may improve tolerance of oral fluids, reduce the need for IV hydration, and potentially reduce hospitalization. Recommendations regarding ondansetron use in children with AGE are not uniform across professional societies. The Canadian Paediatric Society supports consideration of a single oral dose in children with suspected AGE who have persistent vomiting with mild-to-moderate dehydration or who have failed ORT, whereas European guidance has been more cautious regarding routine use because of concerns about adverse effects, particularly diarrhea [3,4]. Thus, current guidance generally emphasizes selective use in appropriately selected children rather than universal administration to all children with AGE.

Ondansetron exerts its antiemetic effects primarily through selective antagonism of 5-HT3 receptors in the GI tract and CNS. During AGE, intestinal inflammation and mucosal stimulation can promote serotonin release from enterochromaffin cells, activating 5-HT3 receptors on vagal afferent pathways and contributing to the vomiting reflex. By blocking these receptors, ondansetron inhibits serotonin-mediated signaling involved in the vomiting reflex, thereby reducing vomiting and facilitating successful oral rehydration. Unlike several other antiemetic agents, ondansetron has minimal activity at dopamine, histamine, and muscarinic receptors, which may contribute to its relatively limited sedative and extrapyramidal effects. However, its use may be associated with adverse effects, particularly increased diarrhea, while QT-interval prolongation remains an important safety consideration, especially in susceptible patients [5-7].

To assess baseline illness severity, evaluate dehydration, and characterize ED triage acuity in children with AGE, clinical studies employ several standardized assessment instruments [8-12]. The Modified Vesikari Scale (MVS) [8] is a composite scoring system ranging from 0 to 20 points that quantifies the severity of gastroenteritis based on the duration and frequency of vomiting and diarrhea, maximum body temperature, health care utilization, and rehydration requirements. Dehydration severity is assessed using validated clinical tools, including the Clinical Dehydration Scale [9], a four-item instrument with scores ranging from 0 to 8, and the Gorelick dehydration scale [10], which uses clinical signs to identify varying degrees of dehydration. The World Health Organization (WHO) [11] dehydration assessment criteria provide an additional standardized approach to classifying dehydration as absent, some, or severe. Furthermore, the Emergency Severity Index [12] is a five-level triage system used in EDs to prioritize patients according to clinical urgency and anticipated resource requirements, with applications in pediatric emergency care. Collectively, these instruments facilitate the standardized assessment of disease severity, dehydration status, and health care needs across pediatric AGE studies.

Several randomized controlled trials (RCTs) and observational studies have evaluated ondansetron in pediatric AGE, with evidence suggesting reductions in vomiting and IV fluid requirements. However, important uncertainties remain regarding its broader clinical effects and safety. In particular, the available evidence varies with respect to dosing strategies, including repeated outpatient dosing, and concerns remain regarding diarrhea and other adverse events. In addition, findings regarding hospitalization, ED revisits, and other healthcare utilization outcomes have been inconsistent across clinical settings and study designs. Observational studies may also provide complementary evidence regarding real-world prescribing and healthcare utilization that is not fully captured by randomized trials. Accordingly, an updated synthesis of the available evidence is warranted to integrate efficacy and safety findings across both randomized and observational studies. This systematic review aimed to evaluate the efficacy and safety of ondansetron, when used as an adjunct to supportive care and ORT, in children with AGE, with particular emphasis on vomiting, oral and IV fluid requirements, adverse events, repeated dosing, ED revisits, hospitalization, and other healthcare utilization outcomes. By incorporating evidence from different study designs and clinical settings, this review seeks to clarify the established benefits of ondansetron while identifying remaining uncertainties relevant to clinical practice and future research.

Review

Methods

Study Design

The PRISMA 2020 guidelines were followed for this systematic review [13]. The review protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261462969. The review aimed to assess the effectiveness and safety of ondansetron for AGE in children and adolescents by summarizing evidence on clinical effectiveness, healthcare utilization, hospital outcomes, and adverse events.

Search Strategy

An electronic literature search was performed in PubMed, Embase, Scopus, the Cochrane Library, and ClinicalTrials.gov from inception to June 2026. Medical Subject Headings (MeSH) and free-text terms relating to AGE, acute intestinal infection, vomiting, children, pediatric, ondansetron, antiemetic, ORT, IV

rehydration, hospitalization, and ED revisits were used. Boolean operators "AND" and "OR" were used to combine the search terms. We also manually searched the reference lists of eligible articles and relevant systematic reviews for potentially eligible studies not retrieved by the electronic search. Details of the search strategies are provided in Appendix A.

Eligibility Criteria

Eligibility criteria were established a priori according to the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework. Studies were eligible for inclusion if they met all of the following criteria: (1) population: children and adolescents aged six months to 18 years with a clinical diagnosis of AGE associated with acute-onset vomiting, with or without diarrhea, recruited from EDs, out-of-hours primary care settings, or pediatric inpatient wards; (2) intervention: ondansetron administered orally or intravenously, including orally disintegrating tablets (ODTs), oral solutions or syrups, single-dose or multiple-dose regimens, or prescriptions for use after discharge; (3) comparator: placebo, ORT, usual care without antiemetic therapy, or no antiemetic treatment; (4) outcomes: at least one relevant clinical efficacy, healthcare utilization, hospitalization, or safety outcome, including vomiting frequency or cessation, disease severity, successful oral rehydration or oral rehydration solution (ORS) tolerance, IV fluid administration, hospital admission, length of hospital stay, ED revisits, or adverse events; (5) study design: comparative primary clinical studies, including RCTs, pragmatic or unblinded RCTs, double-blind placebo-controlled RCTs, and prospective or retrospective comparative cohort studies; (6) publication type: full-text original research articles published in peer-reviewed journals; and (7) language: English.

Studies were excluded if they met any of the following criteria: (1) non-comparative studies: case reports, case series, descriptive observational studies without a comparator group, and other non-comparative studies; (2) non-primary publications: narrative reviews, systematic reviews, meta-analyses, guidelines, consensus statements, editorials, letters, commentaries, study protocols, conference abstracts, and statistical analysis plans; (3) duplicate or overlapping publications: secondary analyses or publications involving overlapping patient populations from previously included studies that did not provide additional relevant outcome data; (4) ineligible intervention: studies evaluating antiemetic agents other than ondansetron without a separate eligible ondansetron treatment arm, or studies in which ondansetron was not administered as part of the intervention; (5) ineligible population or diagnosis: studies involving patients outside the predefined age range or patients with vomiting attributable primarily to non-gastroenteritis causes, including suspected surgical abdomen, bowel obstruction, appendicitis, CNS disorders, or other noninfectious causes; (6) severe clinical instability: studies exclusively involving children with severe dehydration, shock, sepsis, severe malnutrition, or other conditions requiring immediate resuscitation before administration of the study intervention; (7) major underlying comorbidities: studies exclusively involving populations with severe chronic medical conditions that could substantially affect vomiting, dehydration, treatment response, or safety outcomes, including major GI, neurological, renal, or complex congenital cardiac disorders; (8) specific safety-related exclusions: studies exclusively involving participants with known congenital long-QT syndrome, clinically significant baseline cardiac arrhythmias, or other major contraindications to ondansetron; and (9) prior antiemetic exposure: studies in which participants had received another antiemetic medication immediately before enrollment and this exposure could not be separated between treatment groups or could substantially influence study outcomes.

Study Selection and Screening

All retrieved records were transferred to Zotero for reference management and duplicate removal. Following deduplication, the remaining records were uploaded to Rayyan for title and abstract screening. Two reviewers (KB and OC) independently screened all records at the title and abstract stage and subsequently assessed the full texts of potentially eligible reports according to the a priori eligibility criteria. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer (BM). Reasons for exclusion at the full-text stage were documented.

Data Extraction

Two reviewers (MTBR and RS) extracted data independently using a pretested, standardized data extraction form. Extracted information included the first author, year of publication, country, study design, healthcare setting, number of participants, participant demographics, dehydration status, intervention characteristics (ondansetron formulation, dose, route, and treatment regimen), comparator, and follow-up duration. Outcome data included vomiting frequency or cessation of vomiting, severity of illness (such as the Modified Vesikari Score, when available), successful use of ORT, consumption of ORS, use of IV fluids, hospital admission, return to the ED, healthcare utilization, hospital stay, healthcare costs when reported, and complications such as diarrhea and serious adverse events. Where available, effect estimates, including ORs, risk ratios (RRs), HRs, and mean differences (MDs), together with their corresponding 95% CIs, were extracted. For dichotomous outcomes, event and total participant data were also extracted when reported. Discrepancies between reviewers were resolved through discussion and, when necessary, consultation with a third reviewer (FZ).

Risk of Bias and Quality Assessment

RCTs were assessed independently using the Cochrane Risk of Bias 2 (RoB 2) tool [14]. Comparative observational cohort studies were assessed using the Newcastle-Ottawa Scale (NOS) [15]. The NOS was selected because it is a widely used structured tool for assessing the methodological quality of comparative observational cohort studies, including key domains of selection, comparability, and outcome assessment. Studies that received 7-9 stars on the NOS were deemed high quality, 5-6 stars moderate quality, and ⩽4 stars low quality. Risk-of-bias assessments were performed independently, with disagreements resolved through discussion and consensus or consultation with a third reviewer when necessary.

Outcomes

Key efficacy measures were the number of vomiting episodes and whether vomiting ceased; the number of moderate-to-severe cases, defined by validated clinical disease severity scales (MVS, if available); and the success of ORT. Utilization outcomes included IV fluid use, hospital admission, ED revisits, length of hospital stay, and healthcare costs, if reported. Adverse events of treatment, including diarrhea, cardiac arrhythmias, extrapyramidal reactions, and other serious adverse events, were reported as safety outcomes. Potential masking or delay of alternative diagnoses was also considered a safety concern when reported.

Successful ORT was defined according to the criteria reported by each individual study, generally reflecting the ability to tolerate and complete oral fluid administration without requiring IV hydration. Vomiting cessation was defined according to each study's prespecified time point or criterion for the absence of further vomiting episodes. Moderate-to-severe disease was defined using the validated clinical severity criteria or severity scale applied in the respective study. Because outcome definitions and assessment time points varied across studies, the original study-specific definitions were retained during data extraction and narrative synthesis to avoid introducing post hoc definitions and preserve the comparability of findings within each study.

Statistical Analysis and Data Synthesis

A quantitative meta-analysis was not performed because of substantial clinical and methodological heterogeneity across the included studies. Specifically, the studies differed in study design, participant characteristics and dehydration status, ondansetron formulation, dose, route and dosing regimen, comparator groups, follow-up duration, and definitions and measurement methods for the reported outcomes. Furthermore, the reported outcomes were assessed using different clinical definitions and effect measures, limiting the validity and interpretability of pooled estimates. Therefore, a qualitative narrative synthesis was considered more appropriate than statistical pooling. The qualitative narrative synthesis was conducted within four prespecified domains: clinical efficacy, healthcare utilization, hospital outcomes, and safety. Findings were synthesized descriptively. Where available, reported effect estimates (ORs, RRs, HRs, and MDs) with corresponding 95% CIs, as well as event/total data, were summarized narratively without calculating pooled estimates.

Results

Study Selection Process

Database and register searches identified 1,521 records in total. After removal of 469 duplicate records, 1,052 records remained for title and abstract screening. Of these, 687 records were excluded, and 365 reports were sought for retrieval. Two reports could not be retrieved, leaving 363 reports for full-text assessment. Of these, 355 reports were excluded for the following reasons: wrong population (n = 134), wrong intervention (n = 98), wrong outcomes (n = 64), wrong comparator (n = 48), and conference abstracts or abstract-only publications (n = 11). Ultimately, eight studies met the prespecified eligibility criteria and were included in the systematic review. The study selection process is summarized in the PRISMA 2020 flow diagram (Figure *1*).

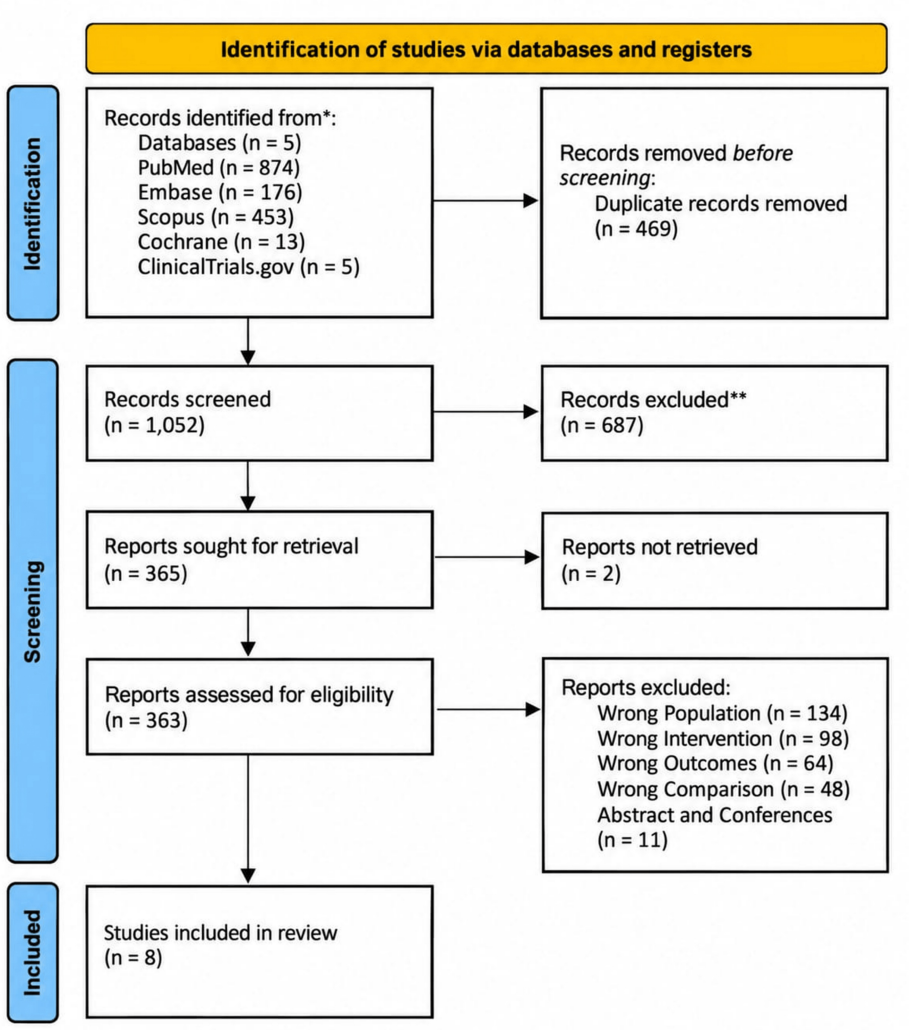


FIGURE 1: PRISMA flow diagram.

* Indicate records identified during the screening process.

** Indicate records excluded during the eligibility assessment.

Baseline Characteristics and Patient Demographics

A total of eight independent primary comparative studies met all eligibility criteria, representing 60,191 unique pediatric patients with AGE. By study design, five RCTs evaluated 2,397 participants (4.0% of the overall sample), ranging from 61 patients in an inpatient ward setting to 1,029 patients across multicenter EDs. Three retrospective comparative cohort studies evaluated 57,794 participants (96.0% of the overall sample), ranging from 339 patients in a single-center pediatric ED to 45,670 patients in a large multisite healthcare database subgroup [16-23]. The study populations consisted predominantly of young children, with reported median or mean ages ranging from 14 months to 4.3 years. Sex distribution was generally balanced across the included studies, although some studies demonstrated modest differences between intervention and control groups. In the RCTs, male participants accounted for approximately 45.0-67.0%, while female participants accounted for 33.0-55.0%. Across comparative cohort studies, sex distribution was similarly balanced between groups. The studies evaluated different ondansetron regimens, including oral solution, oral syrup, ODTs, and IV administration, with doses ranging from 0.1 to 0.2 mg/kg or weight-based fixed doses. Control groups received matching placebo, ORT alone, or no antiemetic treatment. Baseline vomiting severity varied across studies, with reported frequencies ranging from a median of four to nine episodes per 24 hours, while the study by Çelik et al. (2026) [16] reported a mean of approximately 3.7-3.8 episodes. The duration of vomiting at presentation ranged from approximately 13.9 hours to two days in studies reporting this parameter. Diarrhea was common among enrolled participants, with reported baseline prevalence ranging from 32.7% to 100%. Dehydration severity also varied, with studies reporting clinical dehydration scores, Gorelick scores, or clinical classifications ranging from mild to moderate dehydration. The study by Freedman et al. (2019) [20] reported that all participants had some degree of dehydration

according to WHO criteria, while the study by Rang et al. (2019) [19] reported mild dehydration in 87% of participants and moderate dehydration in 13%, as summarized in Table *1*.

Author	Study design and setting	N	Age	Male, n (%)	Female, n (%)	Ondansetron intervention	Comparator	Vomiting duration at baseline	Baseline vomiting frequency	Baseline diarrhea	Dehydration status at enrollment
Çelik et al. (2026) [16]	Retrospective comparative cohort; pediatric ED, Istanbul, Türkiye	339	Median 2.4 years (intervention)/2.5 years (control)	46.0/48.0	54.0/52.0	Single oral dose, 0.15 mg/kg	No antiemetic treatment	Mean 17 ± 6 hours/18 ± 7 hours	Mean 3.7 ± 1.2/3.8 ± 1.3 episodes	100%	NR
Freedman et al. (2025) [17]	Multicenter, double-blind RCT; six Canadian pediatric EDs	1,029	Median 47.5 months (IQR 22.4-80.4)	508 (49.4)	521 (50.6)	Oral solution, 0.15 mg/kg (maximum 8 mg); up to six doses for home use	Matching placebo solution	Median 13.9 hours (IQR 8.9-25.7)	Median maximum 8 episodes/24 hours	32.70%	Median CDS 1 (IQR 0-2); median MVS 9 (IQR 7-10)
Weghorst et al. (2021) [18]	Pragmatic RCT; three out-of-hours primary care centers, Netherlands	175	Median 1.5 years (IQR 0.9-2.1)	87 (49.7)	88 (50.3)	Single oral syrup dose, 0.1 mg/kg	ORT alone (usual care)	Median 2.0 days (IQR 1.0-3.0)	Median 5.0 episodes/24 hours	71.30%	Median GP-assessed dehydration 20.0% (IQR 10.0-40.0)
Rang et al. (2019) [19]	Double-blind RCT; pediatric ward, South Vietnam	61	Median 14 months/17 months	67.0/45.0	33.0/55.0	Single IV bolus, 0.2 mg/kg	IV placebo (0.9% saline)	NR	Median 4.0 episodes/4 hours	100%	87% mild/13% moderate dehydration
Freedman et al. (2019) [20]	Double-blind RCT; two pediatric EDs, Karachi, Pakistan	918	Median 18.0 months	58.7/61.2	41.3/38.8	Single oral ODT dose: 2 mg (8-15 kg) or 4 mg (>15 kg)	Identical placebo ODT	Median 1.0 day (IQR 1-2)	Median 4.0 episodes/24 hours	100%	100% had some dehydration (WHO); median CDS 2
Freedman et al. (2006) [21]	Double-blind RCT; pediatric ED, Chicago, USA	214	Mean 26 ± 21/30 ± 20 months	56.0/58.0	44.0/42.0	Single oral ODT dose: 2, 4, or 8 mg according to weight	Placebo ODT	NR	Mean 9.0 ± 6.0/9.3 ± 6.8 episodes/24 hours	100%	Mean score 11 ± 2 (range 9-16; maximum 21)
Benary et al. (2020) [22]	Retrospective comparative cohort; pediatric ED and 11 UCCs, USA	45,670	Median 4.0 years	49.6/51.0	50.4/49.0	Ondansetron prescription at discharge	No prescription	NR; 55.1% received ED-dose ondansetron	NR	100%	ESI level 4: 68.2%/75.7%
McLaren et al. (2021) [23]	Retrospective comparative cohort; tertiary urban pediatric ED, USA	11,785	Median 4.3 years/3.1 years	51.5/52.2	48.5/47.8	Ondansetron prescription at discharge	No prescription	~75% presented within 24 hours of onset	94.7-99.0% vomited at index	45.0-46.0%	Median Gorelick score 2/1

TABLE 1: Study characteristics, baseline characteristics, and patient demographics.

CDS, Clinical Dehydration Scale; ESI, Emergency Severity Index; GP, general practitioner; MVS, Modified Vesikari Scale; NR, not reported; ODT, orally disintegrating tablet; ORT, oral rehydration therapy; RCT, randomized controlled trial; UCC, urgent care center

Risk of Bias Assessment (RoB 2)

The five RCTs were evaluated for risk of bias using RoB 2. In total, four studies [17,19-21] were rated as having an overall low risk of bias across the five RoB 2 domains. The overall rating for Weghorst et al. (2021) [18] was "some concerns," with concerns in Domain 2 (bias due to deviations from intended interventions) and Domain 4 (bias in measurement of the outcome); the remaining domains were rated as low risk. For all included RCTs, 100% of studies had a low risk of bias in the following domains: randomization process (D1), missing outcome data (D3), and selection of the reported result (D5). Conversely, 4/5 (80%) of studies were assessed as having a low risk of bias in two domains: deviations from intended interventions (D2) and measurement of the outcome (D4), while 20% (1/5) raised some concerns in both domains. Overall, the included randomized trials had high methodological quality, with 80% (4/5) rated as having a low overall risk of bias and 20% (1/5) rated as having some concerns, as shown in Figures *2*, *3*.

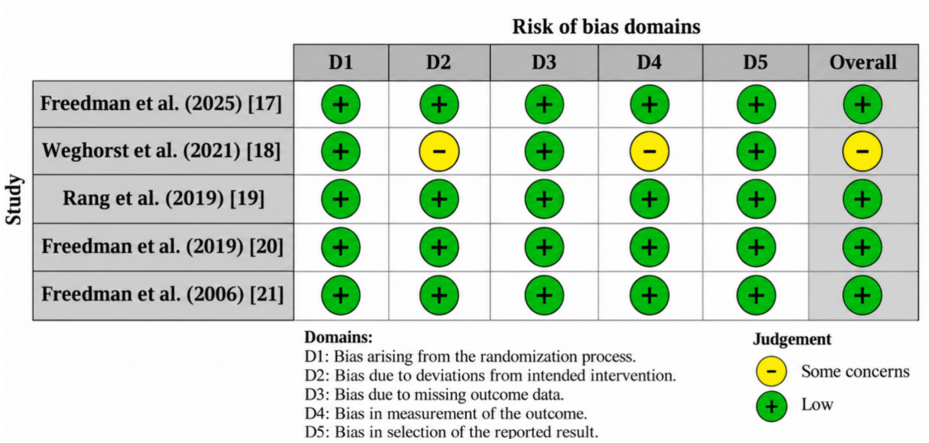


FIGURE 2: Traffic light plot of domains showing risk of bias for included studies using RoB 2.

RoB 2, Risk of Bias 2

[17-21]

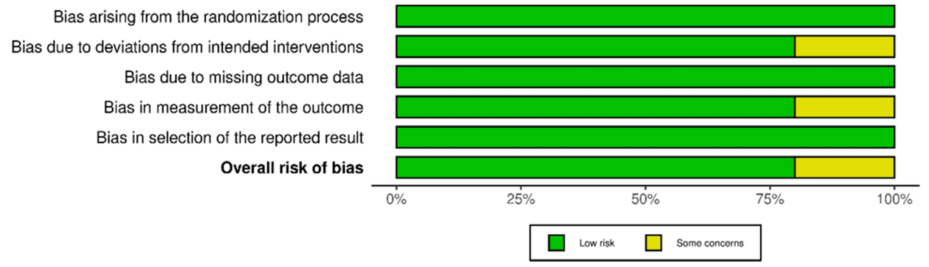


FIGURE 3: Traffic light plot summary for included studies using RoB 2.

RoB 2, Risk of Bias 2

Newcastle-Ottawa Quality Assessment Scale for Retrospective Studies

The methodological quality of the three retrospective cohort studies was assessed using the NOS. All three studies demonstrated high methodological quality according to the prespecified criteria, with scores ranging from 7 to 8 out of 9. Çelik et al. (2026) [16] and Benary et al. (2020) [22] each scored 8/9, with one point not awarded for adequacy of follow-up. McLaren et al. (2021) [23] scored 7/9, with points not awarded for the outcome being absent at baseline and for adequacy of follow-up. Overall, all three studies (100%) were classified as high quality according to the predefined NOS thresholds. Nevertheless, a high NOS score does not eliminate the possibility of residual confounding or other limitations inherent to observational study designs. The detailed NOS assessments are presented in Table *2*.

Study ID	Representativeness of exposed cohort (max 1)	Selection of non-exposed cohort (max 1)	Ascertainment of exposure (max 1)	Outcome not present at start (max 1)	Comparability of cohorts (max 2)	Assessment of outcome (max 1)	Follow-up long enough (max 1)	Adequacy of follow-up (max 1)	Total score (max 9)
Çelik et al. (2026) [16]	★	★	★	★	★★	★	★	-	8
Benary et al. (2020) [22]	★	★	★	★	★★	★	★	-	8
McLaren et al. (2021) [23]	★	★	★	-	★★	★	★	-	7

TABLE 2: NOS for retrospective cohort studies.

★ Indicates an awarded point; the maximum possible score is nine stars.

NOS, Newcastle-Ottawa Scale

Systematic Review of Outcomes

The outcomes of the included studies are summarized in Table 3.

Author	Outcome	Ondansetron group	Control group	Statistics	Conclusion
Çelik et al. (2026) [16]	IV fluid at revisit	12.30%	25.40%	p = 0.011	Reduced IV fluid requirement
	Hospital admission	2.00%	10.00%	p = 0.003	Reduced hospitalization
	Seven-day ED revisit	18.50%	21.00%	p = 0.412	No significant difference
	Serious adverse events	None	None	-	Safe treatment
Freedman et al. (2025) [17]	Vomiting within 48 hours	Median 0 episodes	Median 0 episodes	Adjusted Rate Ratio 0.76 (95% CI: 0.67-0.87)	Reduced vomiting frequency
	Moderate-to-severe disease	5.1% (23/452)	12.5% (55/441)	Adjusted OR 0.50 (95% CI: 0.40-0.60)	Lower disease severity
	Adverse events	7.00%	7.10%	OR 0.99 (95% CI: 0.61-1.61)	No increase in adverse events
Weghorst et al. (2021) [18]	Continued vomiting	19.5% (15/77)	42.9% (33/77)	OR 0.40 (95% CI: 0.20-0.70); NNT = 4	Significant reduction in vomiting
	Healthcare cost	€488 ± 638	€709 ± 839	Mean cost reduction €221/patient	Reduced total societal costs
Rang et al. (2019) [19]	Persistent vomiting (treatment failure)	26.7% (8/30)	77.4% (24/31)	RR 0.32 (95% CI: 0.16-0.63); p < 0.001	Significantly lower risk of persistent vomiting
	IV rehydration	10% (3/30)	39% (12/31)	RR 0.51 (95% CI: 0.33-0.79); p = 0.009	Reduced IV fluid requirement
	ORS intake	450 mL	350 mL	p = 0.019	Improved oral hydration
	Hospital stay	4 days	4 days	p = 0.828	No significant difference
Freedman et al. (2019) [20]	Vomiting during ED stay	13.20%	26.10%	OR 0.43 (95% CI: 0.31-0.61); p < 0.001	Reduced vomiting
	IV fluids (≥20 mL/kg)	14.70%	19.50%	Adjusted OR 0.70 (95% CI: 0.49-1.00); p = 0.05	Reduced IV fluid use

	Hospitalization >24 h	6.30%	7.20%	OR 0.86 (95% CI: 0.52-1.45)	No significant difference
Freedman et al. (2006) [21]	Vomiting during ORT	14%	35%	RR 0.40 (95% CI: 0.26-0.61); p < 0.001	Reduced vomiting
	IV rehydration	14%	31%	RR 0.46 (95% CI: 0.26-0.79); p = 0.003	Reduced IV fluid requirement
	ED stay	106 ± 53 minutes	120 ± 63 minutes	p = 0.02	Shorter ED stay
	Diarrhea episodes	1.4	0.5	p < 0.001	Mild increase in diarrhea
Benary et al. (2020) [22]	72-hour ED revisit	4.00%	4.80%	Adjusted OR 0.82 (95% CI: 0.72-0.95)	Reduced revisit rate
	Missed appendicitis	0.05%	0.06%	OR 0.97 (95% CI: 0.37-2.18)	No increased diagnostic risk
McLaren et al. (2021) [23]	Hospital admission at revisit	28.00%	26.40%	Adjusted OR 0.81 (95% CI: 0.51-1.27)	No significant difference
	72-hour ED revisit	4.90%	4.00%	Adjusted OR 1.12 (95% CI: 0.92-1.33)	No reduction in revisit
	Serious alternative diagnoses	2.90%	4.30%	Adjusted OR 0.56 (95% CI: 0.20-1.59)	No increased safety concerns

TABLE 3: Summary of clinical outcomes of ondansetron in pediatric AGE.

AGE, acute gastroenteritis; NNT, number needed to treat; ORS, oral rehydration solution; ORT, oral rehydration therapy; RR, risk ratio

Vomiting Control

Five studies [17-21] assessed the incidence, duration, frequency, and cessation of vomiting following ondansetron treatment. Overall, the findings generally favored ondansetron for improving vomiting control in children with AGE. In the study by Freedman et al. (2025) [17], both groups had a median of zero vomiting episodes within 48 hours, with an adjusted rate ratio of 0.76 (95% CI, 0.67-0.87). Moderate-to-severe disease, defined as an MVS score ⩾9, occurred in 5.1% (23/452) of children in the ondansetron group compared with 12.5% (55/441) of those in the control group (adjusted OR, 0.50; 95% CI, 0.40-0.60), suggesting a lower risk of greater disease severity. Weghorst et al. (2021) [18] reported continued vomiting after four hours in 19.5% (15/77) of children receiving ondansetron compared with 42.9% (33/77) of those receiving placebo (OR, 0.40; 95% CI, 0.20-0.70; number needed to treat = 4).

Similarly, in an inpatient pediatric trial, Rang et al. (2019) [19] reported complete cessation of vomiting in 73% (22/30) of children receiving IV ondansetron compared with 23% (7/31) of placebo recipients. The reported relative risk (RR) of 0.32 (95% CI, 0.16-0.63; p < 0.001) indicated a significantly lower risk of persistent vomiting (treatment failure) in the ondansetron group, occurring in 26.7% (8/30) of children compared with 77.4% (24/31) in the placebo group. Freedman et al. (2019) [20] found that vomiting during ED observation occurred in 13.2% (61/462) of ondansetron-treated children compared with 26.1% (119/456) of controls (OR, 0.43; 95% CI, 0.31-0.61; p < 0.001). Likewise, Freedman et al. (2006) [21] reported vomiting during ORT in 14% (15/107) of children receiving ondansetron compared with 35% (37/107) of controls (RR, 0.40; 95% CI, 0.26-0.61; p < 0.001). The mean number of vomiting episodes was also lower in the ondansetron group (0.18 ± 0.11 vs. 0.65 ± 0.30; p < 0.001). Overall, the findings suggest that ondansetron improves vomiting control in children with AGE, although the outcomes and effect measures varied across studies.

IV Fluid Rehydration Requirements

Four studies [16,19-21] assessed the need for IV fluid therapy as an indicator of oral rehydration failure. Across these four comparative studies, ondansetron consistently decreased the need for IV fluids. Çelik et al. (2026) [16] found that 12.3% of the ondansetron group required IV fluids at follow-up, compared with 25.4% of the control group (p = 0.011). Similarly, Rang et al. (2019) [19] found that IV rehydration was required in 10% vs. 39% of participants (RR, 0.51; 95% CI, 0.33-0.79; p = 0.009). Freedman et al. (2019) [20] demonstrated a lower rate of IV fluid administration (⩾20 mL/kg) among ondansetron recipients (14.7% vs. 19.5%; adjusted OR, 0.70; 95% CI, 0.49-1.00; p = 0.05). Likewise, Freedman et al. (2006) [21] reported IV rehydration rates of 14% vs. 31% in controls (RR, 0.46; 95% CI, 0.26-0.79; p = 0.003).

Studies also reported quantitative hydration outcomes. The amount of ORS consumed (239 mL vs. 196 mL; p = 0.001) and the mean quantity of IV fluids administered (38 mL/kg vs. 46 mL/kg; p = 0.002) were lower in the ondansetron group. Rang et al. (2019) [19] also demonstrated higher median 24-hour ORS intake (450 mL vs. 350 mL; p = 0.019). Overall, this evidence suggests that ondansetron can facilitate oral rehydration and reduce the need for IV fluid therapy.

Hospital Admission Outcomes

Six studies [16,18-21,23] evaluated hospital admission and hospitalization outcomes. Results tended to favor ondansetron but were not always statistically significant. Çelik et al. (2026) [16] showed a significantly lower hospital admission rate in the ondansetron group (2.0% vs. 10.0%; p = 0.003). In contrast, Freedman et al. (2019) [20] reported similar hospitalization rates for stays exceeding 24 hours (6.3% vs. 7.2%; OR, 0.86; 95% CI, 0.52-1.45), while Freedman et al. (2006) [21] observed no difference in admission rates (4% vs. 5%; RR, 0.80; 95% CI, 0.22-2.90; p = 1.00). McLaren et al. (2021) [23] similarly found no significant difference in hospital admission at revisit (28.0% vs. 26.4%; adjusted OR, 0.81; 95% CI, 0.51-1.27).

Freedman et al. (2006) [21] reported a significantly shorter ED stay (106 ± 53 vs. 120 ± 63 minutes; p = 0.02), whereas Rang et al. (2019) [19] reported no difference in median hospital stay (four vs. four days; p = 0.828). Weghorst et al. (2021) [18] also reported lower healthcare costs, with mean total healthcare costs of €488 ± 638 in the ondansetron group compared with €709 ± 839 in the control group, representing a reduction of €221 per patient. Overall, ondansetron may reduce hospitalization in some settings and improve healthcare efficiency, but the evidence regarding length of stay is mixed.

ED Return Visits

Three studies [16,22,23] assessed post-discharge healthcare utilization through ED revisit rates. The results were mixed. Benary et al. (2020) [22] reported a significantly lower rate of ED revisits within 72 hours among children receiving ondansetron (4.0% vs. 4.8%; adjusted OR, 0.82; 95% CI, 0.72-0.95). The ondansetron group also had fewer unscheduled healthcare visits within seven days than the control group (9.3% vs. 13.2%; adjusted OR, 0.67; 95% CI, 0.44-1.02), although the CI included 1. Conversely, McLaren et al. (2021) [23] found no significant reduction in 72-hour revisits (4.9% vs. 4.0%; adjusted OR, 1.12; 95% CI, 0.92-1.33), and Çelik et al. (2026) [16] similarly reported comparable seven-day revisit rates (18.5% vs. 21.0%; p = 0.412). Overall, the evidence regarding ondansetron's effect on ED revisit rates is inconclusive.

Safety Outcomes

The safety profile of ondansetron was assessed in five studies [16,17,21-23]. Overall, ondansetron was generally well tolerated, with no clear increase in major adverse events. No difference in the overall adverse-event rate (7.0% vs. 7.1%; OR, 0.99; 95% CI, 0.61-1.61) was observed between the two treatment groups in the study by Freedman et al. (2025) [17]. Diarrhea was the most common adverse event. Children who received three or more doses of ondansetron had increased stool frequency (rate ratio, 1.36; 95% CI, 1.03-1.80; p = 0.03). Likewise, Freedman et al. (2006) [21] found a higher mean number of diarrhea episodes in the ED (1.4 vs. 0.5; p < 0.001).

Serious complications were uncommon. Benary et al. (2020) [22] found no increased risk of missed appendicitis (0.05% vs. 0.06%; OR, 0.97; 95% CI, 0.37-2.18). McLaren et al. (2021) [23] reported no increase in alternative serious diagnoses (2.9% vs. 4.3%; adjusted OR, 0.56; 95% CI, 0.20-1.59), and Çelik et al. (2026) [16] reported no arrhythmias, extrapyramidal reactions, or other serious complications in either group. Overall, the available evidence suggests that ondansetron is generally well tolerated, with no clear evidence of an increased risk of serious adverse events; mild, transient diarrhea was the main adverse event reported.

Discussion

Summary of Findings

This systematic review aimed to assess the clinical efficacy, health service use, hospital outcomes, and safety of ondansetron in children with AGE. Overall, the results suggest that ondansetron may be beneficial for controlling vomiting and facilitating oral rehydration. Across the comparative studies, ondansetron was associated with fewer vomiting episodes or longer vomiting-free periods, and several studies reported reduced use of IV fluid therapy. However, findings regarding hospitalization and subsequent ED or healthcare revisits were inconsistent, with some studies reporting reductions and others showing no statistically significant differences. Safety outcomes were generally reassuring, with no meaningful increase in serious adverse events, although an increase in diarrhea, particularly with repeated dosing, was observed in some studies. Therefore, the most consistent potential clinical benefit of ondansetron appears to be improved vomiting control and oral rehydration, whereas its effects on downstream healthcare utilization and hospital outcomes remain uncertain. Given the heterogeneity of the included studies and the absence of quantitative meta-analysis, these findings should be interpreted as an overall synthesis of the available evidence rather than as definitive estimates of treatment effectiveness.

Comparison With Previous Literature

The current review found a significant improvement in vomiting, consistent with earlier findings. One study found that ondansetron improved the likelihood of rapid cessation of vomiting after treatment, indicating that it may help reduce the immediate burden of emesis in children with AGE [24]. A revised meta-analysis found a higher likelihood of vomiting cessation within the first few hours after a single dose of ondansetron [25]. Another study evaluating several antiemetic medications found that ondansetron had the strongest evidence for reducing vomiting episodes and achieving vomiting cessation [26]. These findings are consistent with those of the current review and suggest that ondansetron's antiemetic effect is one of its most consistent treatment effects in pediatric gastroenteritis.

Furthermore, the reduction in vomiting is clinically significant because vomiting can impede oral rehydration and increase the likelihood of IV fluid administration. In the current review, lower IV fluid requirements were consistently reported across the relevant studies, along with improved tolerance of ORS. Previous evidence supports this association. A systematic review found that ondansetron substantially reduced the need for IV rehydration in children with AGE [24]. Similarly, another study found significant reductions in IV hydration requirements and oral rehydration failure after ondansetron treatment [25]. Moreover, one study found that ondansetron decreased the need for IV fluids [27]. These findings suggest that ondansetron's benefits extend beyond vomiting suppression, as improved control of emesis may facilitate continued oral fluid intake and reduce the need for more invasive rehydration.

Findings regarding subsequent ED and healthcare revisits were heterogeneous. Some studies reported fewer subsequent visits among children receiving ondansetron, whereas others found no statistically significant differences. This variability is also reflected in previous research. A previous comprehensive analysis reported no significant difference in return ED visits despite benefits in vomiting control and IV fluid requirements [27], and a meta-analysis of single-dose ondansetron similarly found no statistically significant difference in ED return visits [25]. Conversely, one observational study reported fewer 72-hour ED revisits among children receiving discharge prescriptions for ondansetron [28]. The inconsistency across studies may reflect differences in study design, healthcare setting, discharge practices, follow-up periods, access to outpatient care, persistence of diarrhea, and parental concern rather than a direct effect of ondansetron itself. Because ED revisits were not consistently reduced across studies, the evidence does not support the conclusion that ondansetron reliably decreases subsequent healthcare utilization.

The safety findings of this review were generally reassuring. No significant increase in serious adverse events was observed, and diarrhea was the most commonly reported treatment-related adverse event. Previous research has similarly identified diarrhea as an important adverse effect of ondansetron in pediatric gastroenteritis [27]. The available evidence does not indicate a major short-term safety signal that would outweigh its potential clinical benefits. However, evidence regarding long-term safety remains limited, and the available studies were not designed to establish long-term safety outcomes [25]. Increased diarrhea is clinically relevant because diarrhea is already a major component of AGE; nevertheless, the available evidence does not suggest that this increase commonly results in serious clinical deterioration. The present review also found no clear evidence of an increased risk of missed serious diagnoses among children receiving ondansetron. However, these findings should be interpreted cautiously because evidence regarding the masking of alternative diagnoses is derived primarily from observational data and cannot completely exclude uncommon events [28-32].

The potential effects of ondansetron on healthcare efficiency also warrant cautious interpretation. Although several studies reported reduced IV fluid use and improved tolerance of oral rehydration, the inconsistent findings regarding hospitalization and ED revisits indicate that reductions in resource utilization cannot be assumed across all healthcare settings. Similarly, reported economic benefits should be considered preliminary because relatively limited economic evidence was available, and differences in healthcare systems, costs, prescribing practices, and resource utilization may limit generalizability [25,27,30,31]. Ondansetron should therefore be considered an adjunct to oral rehydration rather than a substitute for fluid therapy. Its most consistent potential benefit appears to be improved vomiting control and facilitation of oral hydration, whereas its effects on broader healthcare utilization remain uncertain.

Overall, the available evidence suggests that ondansetron may be a useful adjunct to oral rehydration in appropriately selected children with AGE, particularly for reducing vomiting and facilitating oral fluid intake. However, its effects on hospitalization and ED revisits were inconsistent, and the absence of quantitative synthesis limits the ability to estimate the magnitude and precision of treatment effects. Safety findings were generally reassuring in the short term, although diarrhea remains an important adverse effect and evidence regarding long-term safety is limited. These findings support the selective use of ondansetron in appropriate clinical settings while highlighting the need for further high-quality randomized evidence.

Future Directions

There is substantial evidence supporting the short-term antiemetic effect of ondansetron, but several questions remain unanswered. More RCTs are needed to compare different dosing regimens, routes of

administration, and repeated-dose strategies, with adequately powered follow-up to evaluate safety beyond the acute treatment period. Comparability would be enhanced by standardized outcome definitions, particularly for oral rehydration success, hospital admission, and ED revisits. Further studies are needed to determine whether there are populations in which ondansetron is most likely to be beneficial, such as infants, children with more severe dehydration, and those treated in primary care settings. Future studies should also prospectively evaluate hospitalization and ED revisits using standardized definitions and follow-up periods. In addition, well-designed cost-effectiveness analyses across different healthcare systems and implementation studies would help clarify the broader healthcare and economic implications of ondansetron use.

Strengths

This systematic review has several important strengths. It followed the PRISMA 2020 guidelines and used a systematic search of several databases to minimize the risk of missing relevant studies. The inclusion of RCTs and retrospective cohort studies provided evidence from both controlled research and real-world clinical practice. To ensure the reliability of the results, the methodological quality of the included studies was carefully evaluated using validated instruments, such as the Cochrane RoB 2 tool and the NOS. In addition, this review assessed a wide range of outcomes, including clinical effectiveness, healthcare utilization, hospital outcomes, and safety, providing a comprehensive analysis of ondansetron use in pediatric AGE. The inclusion of studies from various countries and healthcare settings also enhances the generalizability of the conclusions.

Limitations

This review had several limitations. Significant variability among the included studies in study design, patient population, ondansetron dosage regimen, route of administration, outcome definitions, and follow-up duration precluded quantitative meta-analysis and limited direct comparisons across studies. The review was restricted to English-language, peer-reviewed publications, creating a risk of language and publication bias. Furthermore, some included studies were retrospective cohort studies, which are more susceptible to selection bias and confounding than RCTs. Therefore, associations observed in the observational studies should not be interpreted as definitive evidence of causality or treatment effectiveness. Evidence regarding hospital admissions, ED revisits, and long-term safety outcomes was inconclusive. The limited availability of long-term and economic data also prevented firm conclusions regarding the long-term safety or cost-effectiveness of ondansetron. Lastly, most studies were conducted in EDs and involved children with mild to moderate dehydration, so the results may not apply to primary care settings, severe dehydration, or children with significant comorbidities.

Conclusions

This systematic review suggests that ondansetron may be an effective adjunct to oral rehydration in appropriately selected children with AGE, particularly for reducing vomiting and facilitating oral rehydration, with several studies also reporting reduced IV fluid requirements. However, evidence regarding hospital admissions and ED revisits was inconsistent. Short-term safety findings were generally reassuring, although diarrhea was an important treatment-related adverse effect, particularly with repeated dosing, and evidence regarding long-term safety remains limited. Given the heterogeneity of the included studies, the inclusion of observational evidence, and the absence of quantitative meta-analysis, the magnitude of these potential benefits and their effects on broader healthcare utilization remain uncertain. Economic findings should likewise be interpreted cautiously because of limited evidence and differences across healthcare systems. Further high-quality randomized studies with standardized outcomes and longer follow-up are needed to clarify the comparative effectiveness, long-term safety, and economic implications of ondansetron in pediatric AGE.

Appendices

Appendix A

Database	Number of records	Search strategy
PubMed	874	("Ondansetron"[MeSH Terms] OR "Ondansetron"[Title/Abstract] OR "zofran"[Title/Abstract]) AND ("Gastroenteritis"[MeSH Terms] OR "Gastroenteritis"[Title/Abstract] OR "acute gastroenteritis"[Title/Abstract] OR "diarrh*"[Title/Abstract] OR "vomiting"[Title/Abstract] OR "emesis"[Title/Abstract] OR "viral gastroenteritis"[Title/Abstract]) AND ("Child"[MeSH Terms] OR "Infant"[MeSH Terms] OR "Adolescent"[MeSH Terms] OR "pediatric*"[Title/Abstract] OR "paediatric*"[Title/Abstract] OR "child*"[Title/Abstract] OR "infant*"[Title/Abstract] OR "toddler*"[Title/Abstract] OR "adolescent*"[Title/Abstract] OR "newborn*"[Title/Abstract] OR "neonat*"[Title/Abstract])
Embase	176	('ondansetron'/exp OR ondansetron:ti) AND ('acute gastroenteritis':ti OR gastroenteritis:ti) AND ('child'/exp OR 'infant'/exp OR pediatric:ti OR paediatric:ti OR child:ti OR infant:ti)
Scopus	453	(TITLE-ABS-KEY (ondansetron OR zofran) AND ALL (acute gastroenteritis OR gastroenteritis) AND ALL (child OR pediatric OR paediatric OR infant OR toddler OR adolescent))
Cochrane	13	#1 MeSH descriptor: [Ondansetron] explode all trees; #2 ondansetron:ti,ab,kw OR zofran:ti,ab,kw; #3 #1 OR #2; #4 MeSH descriptor: [Gastroenteritis] explode all trees; #5 "acute gastroenteritis":ti,ab,kw OR gastroenteritis:ti,ab,kw; #6 #4 OR #5; #7 MeSH descriptor: [Child] explode all trees; #8 MeSH descriptor: [Infant] explode all trees; #9 MeSH descriptor: [Adolescent] explode all trees; #10 child:ti,ab,kw OR children:ti,ab,kw OR pediatric:ti,ab,kw OR paediatric:ti,ab,kw OR infant:ti,ab,kw OR toddler:ti,ab,kw OR adolescent:ti,ab,kw; #11 #7 OR #8 OR #9 OR #10
ClinicalTrials.gov	5	Search field: Condition or disease; search term: Acute Gastroenteritis OR Gastroenteritis; other terms: Ondansetron; study type: Interventional Studies (Clinical Trials); age: Child (birth–17 years); status: All studies; results: All; language: No filter

TABLE 4: Databases, numbers of records, and search strategies retrieved for the systematic review.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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