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SUMMARY WITH CRITICAL APPRAISAL

Ondansetron and Oral Rehydration Therapy in Pediatric Patients with Dehydration: A Review of Clinical Effectiveness

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Abbreviations

NNT	number needed to treat
ORS	oral rehydration solution
ORT	oral rehydration therapy
RCT	randomized controlled trial
WHO	World Health Organization

Context and Policy Issues

Dehydration occurs when losses of water and electrolytes are not adequately replaced,[1,2] often secondary to vomiting and diarrhea related to gastroenteritis.[2] Severe dehydration and the resultant decreased blood volume results in decreased tissue perfusion and can cause ischemic end-organ damage if not corrected with fluid repletion.[2] Oral rehydration solution was an important medical advance, resulting in decreased mortality from diarrheal illness.[3]

Several methods of defining and categorizing severity of dehydration have been used in the literature. The World Health Organization (WHO) categorizes dehydration as severe dehydration (two or more signs of severe dehydration), some dehydration (two or more signs of dehydration that are not severe), or no dehydration (not meeting the criteria for some or severe).[1] The Clinical Dehydration Scale is a validated four-item scale categorizing dehydration as mild, moderate or severe according to physical exam findings;[4] the clinical features assessed are appearance, eyes, mucous membranes, and tears. A score between 1 and 4 is considered mild dehydration, whereas a score of 5 to 8 is considered moderate to severe. Dehydration can also be categorized according to percentage of body weight lost; mild dehydration corresponds to a loss of 3% to 5% of body weight, moderate 6% to 9%, and severe 10% or greater.[2,4]

Oral rehydration therapy refers to the frequent administration of small amounts of fluid in order to prevent or treat dehydration. The oral rehydration solution recommended by the WHO contains 75 mEq/L of sodium and 75 mmol/L of glucose, with a total osmolarity of 245 mOsm/L.[3] For severe dehydration, WHO recommends intravenous administration of isotonic fluid as well as oral rehydration therapy with oral rehydration solution if feasible. Oral rehydration therapy (with oral rehydration solution) is recommended for children with some dehydration. Administration of extra oral fluids at home is recommended for children with no dehydration.[1] A number of antiemetics have been studied in children with gastroenteritis, including dexamethasone, dimenhydrinate, domperidone, granisetron, metoclopramide, and ondansetron.[5] Apart from ondansetron, evidence to support the use of other antiemetics in children with acute gastroenteritis is lacking.[5,6]

Ondansetron is a serotonin receptor antagonist, selective for the 5-HT3 subtype. It is indicated for the prevention and treatment of nausea and vomiting related to chemotherapy or radiotherapy, as well as post-operative nausea and vomiting, in children age 4-18 and adults. Ondansetron is available in Canada as an oral solution, tablet, and oral disintegrating tablet (ODT).[7] It is typically well-tolerated; the most common adverse effects include mild headache, asthenia, constipation, and dizziness.[7,8] Although, an increased risk of diarrhea up to 48 hours after administration of ondansetron was the most commonly reported adverse effect in studies of children with gastroenteritis.[9] Ondansetron causes dose-dependent prolongation of the QT-interval, and cases of torsades de pointes have

been reported. Ondansetron should be avoided in patients with congenital long QT syndrome and used with caution in individuals at risk of torsades de pointes.[7]

The Canadian pediatric society recommends considering a single dose of ondansetron for children between 6 months to 12 years old presenting to the emergency department with vomiting related to suspected acute gastroenteritis, and mild to moderate dehydration or failed oral rehydration therapy. They recommend initiation of oral rehydration therapy 15 min to 30 min after administration of oral ondansetron.[9]

The objective of this review was to summarize the evidence surrounding the clinical effectiveness of ondansetron for pediatric patients with or at risk of mild to moderate dehydration. For the purposes of this report, dehydration is categorized as mild to moderate according to the definitions used within the included studies. The population considered to be “at risk” of dehydration includes those who do not meet the criteria for mild or moderate dehydration according to the study definition but in whom oral rehydration therapy is deemed necessary.

Research Question

What is the comparative clinical effectiveness of ondansetron alone or in combination with oral rehydration therapy versus oral rehydration therapy alone for pediatric patients with or at risk of mild to moderate dehydration?

Key Findings

Evidence from three randomized controlled trials in pediatric patients with mild to moderate dehydration secondary to gastroenteritis, suggests that ondansetron is effective for decreasing risk of requiring intravenous rehydration and reducing vomiting as compared to placebo, both in combination with oral rehydration solution. In another RCT in which level of dehydration was not described, ondansetron was not superior to placebo for reduction of vomiting. Evidence from a randomized controlled trial in which children were at risk of but with no dehydration did not find ondansetron to be effective as compared to placebo, both in combination with oral rehydration solution.

Evidence from a non-randomized study among children with mild to moderate dehydration secondary to gastroenteritis who were discharged from the emergency department indicated no difference in returns and readmissions to the emergency department within 72 hours, for patients receiving ondansetron compared to those who did not.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were Ondansetron, pediatrics and dehydration. No filters were applied to limit the retrieval by study type. Where

possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and January 14, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Pediatric patients (between 6 months and 18 years of age) with or at risk of mild to moderate dehydration from any cause **Subgroup of interest: pediatric patients between 6 months and 12 years of age**
Intervention	Ondansetron in any dose (i.e., Zofran) alone or combined with oral rehydration therapy given in hospital or at home
Comparator	Oral rehydration therapy (e.g., all forms, including water, juice, oral rehydration solutions [such as electrolyte solutions, Pedialyte])
Outcomes	Clinical effectiveness (e.g., change in hydration levels, need for intravenous fluids, admission to hospital, re-presentation to emergency room, change in symptoms, safety or harms)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015.

Critical Appraisal of Individual Studies

The included RCTs were critically appraised using the Cochrane RoB2 tool,[10] and the non-randomized study was critically appraised using the Cochrane ROBINS-I tool.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 101 citations were identified in the literature search. Following screening of titles and abstracts, 92 citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. Seven potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 10 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised five RCTs and one non-randomized study. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding characteristics of included publications are provided in Appendix 2.

Study Design

Six primary studies met eligibility criteria. Five were placebo-controlled double-blind RCTs.[13-17] The non-randomized study was a retrospective comparative cohort study.[18]

Country of Origin

Two RCTs were conducted in Pakistan,[13,14] and one each in Vietnam,[15] Sweden,[16] and India.[17]

The non-randomized study was conducted in the United States.[18]

Patient Population

Two RCTs conducted by Freedman et al. in Pakistan included children 0.5 to 5 years old presenting with acute gastroenteritis; one included children with some dehydration[13] (n=981) and one included only children with no dehydration (n=626) according to WHO dehydration severity scale.[14] Both studies included children with at least one episode of vomiting and one episode of diarrhea within four hours prior to triage. The first RCT[13] defined “some” dehydration according to WHO dehydration tool (requires the presence of two or more of the following: restlessness and/or irritability, sunken eyes, drinking eagerly and/or thirst, and skin pinch retracts slowly). Children with severe dehydration were excluded. The median age was 18 months in both the ondansetron and placebo groups. The second RCT by Freedman et al excluded children with dehydration.[14] The median age was 15 months in the ondansetron and 16 months the placebo groups.

Rang et al. included 61 children 11 to 60 months old admitted to the pediatric ward of a hospital in Vietnam with diarrhea and mild to moderate dehydration; 87% were classified as having mild dehydration and 13% moderate.[15] Method of categorizing dehydration as mild or moderate was not described.

Hagbom et al. included 81 children 6 months to 16 years old presenting to a hospital in Sweden.[16] The median age was 24 months in both groups. In both groups 83% of participants had confirmed rotavirus infection. In the ondansetron group 17.5% had confirmed norovirus, and none had both norovirus and rotavirus. In the placebo group 9.8% had norovirus and 7.3% both rotavirus and norovirus. Children with severe dehydration or who had used antiemetics within the past 72 hours were excluded; the baseline level of dehydration or proportion with dehydration was not described.

Danewa et al. included 167 children aged 3 months to 5 years presenting to the pediatric emergency department of a tertiary care hospital in Delhi, India with acute diarrhea, vomiting, and some dehydration according to WHO criteria.[17] Children who had received any antiemetic within past 12 hours, or received IV fluids, were excluded. The mean age was 15.5 months in the ondansetron and 15.0 months in placebo groups. In addition to WHO dehydration severity categorization, baseline dehydration was scored according to a previously published unvalidated scale.[19] Baseline dehydration scores were similar between ondansetron and placebo groups, at 12.5 and 13.1, respectively.

The non-randomized study by McLaren et al. was conducted at a tertiary care urban pediatric emergency department in the United States.[18] They included 11785 children 6 months to 18 years old with vomiting due to gastroenteritis. Median age was 3.1 years in children who received ondansetron and 4.3 in those who did not. Baseline level of dehydration was assessed according to a dehydration scale previously proposed by Gorelick et al, [20] in which a median score of 1 was found among participants with no or mild dehydration (fluid deficit of less than 5% of body weight), and a median score of 5 among participants with moderate dehydration (fluid deficit of 5% to 9%). The median score at baseline in MacLaren et al was 1 in the group that did not receive ondansetron and 2 in the ondansetron group.

Interventions and Comparators

In both RCTs conducted by Freedman et al.,[13,14] children received weight based target volume of oral rehydration solution in accordance with WHO recommendations. Children were randomized to receive a single oral dose of ondansetron ODT (oral disintegrating tablet) or matching placebo. A dose of 2mg (half tablet) was administered to children weighing 8 to 15kg, and 4mg to patients weighing15kg or more. Oral rehydration therapy with oral rehydration solution was initiated 15 minutes after ondansetron or placebo. Children who vomited within 15 minutes of ondansetron administration were given a second dose of ondansetron.

Rang et al. randomized hospitalized children to receive a one-time dose of ondansetron 0.2mg/kg administered intravenously or matching placebo. Both groups additionally received oral rehydration solution administered at a dose of 0.5 mL/kg every 2 minutes with a spoon, glass or cup, to a target of 40mL/kg.[15]

Hagbom et al. randomized children to receive oral ondansetron solution 0.15mg/kg or identical oral placebo solution.[16] Weight-based oral rehydration solution was initiated 15 min after ondansetron or placebo in accordance with WHO recommendations.

Danewa et al. randomized children to receive ondansetron oral solution 0.2mg/kg or placebo.[17] The dose was repeated once if vomiting occurred within 30 minutes of the initial dose. Both groups received oral rehydration therapy at the rate of 75 mL/kg in first four hours. A repeat course of 75 mL/kg of oral rehydration solution over four hours was given to children who continued to have features of some dehydration after the initial four hours of therapy.

McLaren et al. compared children who received a prescription for ondansetron on emergency department discharge to those who did not.[18] An additional comparison was made between children who received ondansetron in the emergency department and those who did not. Dose of ondansetron was not specified. The institution protocol for treatment of acute gastroenteritis includes guidance for oral rehydration therapy; 5-10mL of an oral rehydration solution is offered every 5-10 minutes as tolerated.

Outcomes

In both RCTs conducted by Freedman et al.,[13,14] the primary outcome was intravenous rehydration (defined as the administration 20 mL/kg or more over 4 hours of an isotonic fluid for the purpose of rehydration within 72h). Secondary outcomes included vomiting presence and frequency, hospitalization for greater than 24 hours, volume of ORS consumed, presence of some dehydration after discharge, number of diarrheal stools, and treatment failure. Both RCTs additionally reported serious adverse events.

Similarly, the primary outcome in Rang et al.[15] was need for intravenous rehydration. Secondary outcomes included cessation of vomiting after 4h, number of vomiting episodes, volume (per kg) of oral rehydration solution intake, number of diarrhea episodes, duration of diarrhea, length of hospital stay, and adverse effects of ondansetron.[15]

The primary outcome in Hagbom et al. was number of vomiting and diarrhea episodes at 24h.[16] Secondary endpoints were the number of days with symptoms (diarrhea and/or vomiting); this outcome was introduced later in the study, starting with the 21st participant.

In Danewa et al.,[17] primary outcomes included administration of unscheduled intravenous fluids, failure of ORT (defined as features of some dehydration persisting after 4 hours of ORT or severe dehydration at any time during assessment), and amount of ORS intake. Secondary outcomes were duration of dehydration correction, number of vomiting episodes, adverse effects, and caregiver satisfaction.

The primary outcome in the non-randomized study by McLaren et al. was unscheduled ED visit within 72 hours of discharge.[18]

Summary of Critical Appraisal

Both RCTs conducted by Freedman et al. were deemed to be at low risk of bias,[13,14] as were the RCTs conducted by Hagbom et al.[16] and Danewa et al.[17] All were deemed to have low risk of bias with respect to the domains of randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Although randomization, allocation concealment and blinding were described less thoroughly in Hagbom et al. Participant characteristics were also less well-described in that study; baseline level of dehydration was not provided. With respect to external validity, study locations in Pakistan, Sweden, and India may limit applicability to Canadian context. In both Hagbom et al.[16] and Danewa et al.,[17] analyses were not adjusted for multiple outcome measures despite having multiple primary and secondary endpoints; whereas adjustments for multiple comparisons for secondary outcomes were made in both RCTs by Freedman et al.

The RCT conducted by Rang et al. was found to have some concerns with respect to risk of bias.[15] Randomization and allocation concealment were adequately described. Although it was noted to be double-blind, it was not clear who was blinded. There was no statistical adjustment for multiple outcome measures. Protocol registration or pre-specification of trial methods was not documented. Additionally, study location in an inpatient ward in Vietnam may limit applicability to Canadian context.

The retrospective comparative cohort study by McLaren et al. was deemed to have a critical risk of bias, due to the potential for residual confounding.[18] Additionally, there was no information with respect to adherence to ondansetron or oral rehydration therapy. Statistical analysis methods were not clearly defined a priori, leading to a serious risk of bias with respect to selection of the reported result. A large sample size, clear inclusion and exclusion criteria, and blinded outcome analysis were some strengths of this study.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical effectiveness of ondansetron for dehydration

In the RCT conducted by Freedman et al. in children presenting to Pakistan ERs with some dehydration,[13] 981 children were enrolled. Ondansetron statistically significantly decreased the risk of the primary outcome of requiring intravenous rehydration, as compared to placebo, with a number needed to treat (NNT) of 21. Although statistically significant, the absolute risk reduction of 4.8% did not reach the pre-defined minimally clinically important difference of 10% for the primary outcome. Risk of vomiting and number of vomiting episodes were also statistically significantly decreased with ondansetron as compared to placebo. There was no statistically significant difference in hospitalization, diarrhea, dehydration, volume of oral fluids, or treatment failure. There were no serious adverse events.

In the RCT conducted by Freedman et al. in children without dehydration, 626 children were enrolled.[14] In contrast to the findings of their RCT including children with some dehydration, this RCT found no difference in the primary outcome of requiring intravenous hydration for those receiving ondansetron versus placebo. Risk of vomiting was lower in the ondansetron group with an absolute reduction of 4.3%, however this difference was not statistically significant. The median number of vomiting episodes was 0 in each group. Volume of oral fluids administered per kilogram, hospitalization, presence of dehydration, diarrhea, and treatment failure were also similar between groups. There were no serious adverse events.

In the RCT conducted by Rang et al. in hospitalized children in Vietnam, 61 children were enrolled.[15] A single dose of intravenous ondansetron as compared to placebo statistically significantly decreased risk of requiring intravenous rehydration with an NNT of 4. Additionally, children who received ondansetron were more likely to have complete cessation of vomiting, fewer episodes of vomiting, and increased volume (per kg) of oral rehydration solution intake at 4 and 24 hours. All of these differences were statistically significant. There was no statistically significant difference in duration of diarrhea symptoms, frequency of episodes of diarrhea, or length of hospital stay. Only one adverse event in the ondansetron group was reported.

Hagbom et al. enrolled 81 children.[16] The number of vomiting episodes were similar between in children receiving ondansetron as compared to placebo. The number of diarrheal episodes was lower with ondansetron (median 1.0 vs 3.5), but this difference was not statistically significantly different. Total days with vomiting or diarrhea symptoms was statistically significantly decreased with ondansetron as compared to placebo, with a median 4 vs 6 days.

Danewa et al. enrolled 167 children.[17] Ondansetron decreased risk of failure of ORT with an NNT of 4 as compared to placebo. Volume of ORS intake was statistically significantly increased with ondansetron as compared to placebo. Although risk of receiving intravenous fluid was decreased with ondansetron, the difference was not statistically significant. Number of vomiting episodes in 4 hours and duration of dehydration correction were statistically significantly decreased. Caregiver satisfaction, as assessed in several domains on a Likert scale, was also statistically significantly improved in all fields (mood, activity, alertness, comfort, number of vomiting episodes, fluid intake). There were no adverse effects reported in either group.

In the non-randomized study by McLaren et al.,[18] 4187 of 11785 children with acute gastroenteritis were discharged from the emergency department with a prescription for ondansetron. Ondansetron prescription was associated with a statistically significant increase in return to the emergency department within 72 hours; the odds ratio was adjusted for Emergency Severity Index (ESI), age, insurance source, race, and time of index visit registration. When the analysis was also adjusted for receipt of ondansetron in the emergency department, the association was no longer statistically significant. Similarly, administration of ondansetron in the emergency department was associated with a statistically significant increase in 72 hour readmission. When the analysis was limited to those with dehydration scores, the association was not statistically significant.

Appendix 4 presents a table of the main study findings and authors' conclusions.

Limitations

Five recent RCTs comparing ondansetron to placebo in combination with oral rehydration solution were conducted in Pakistan, Sweden, India, and Vietnam; this may limit applicability to the Canadian context. A non-randomized study was conducted in the United States, however a critical risk of bias due to confounding limits interpretation of results.

Available evidence supporting ondansetron's effectiveness is limited to children with mild to moderate dehydration secondary to acute gastroenteritis. Oral rehydration solution was used for oral rehydration in all the RCTs included in this report. Effectiveness of ondansetron in other settings or in combination with other oral rehydration therapy strategies is uncertain.

Outcome definitions, dosing strategies, and baseline level of dehydration differed between studies. Methods of categorizing and describing dehydration severity were also not consistent across studies.

Conclusions and Implications for Decision or Policy Making

Five RCTs and one non-randomized study were included in this report. Three randomized controlled trials in children with mild to moderate dehydration found ondansetron to be superior to placebo (both in combination with oral rehydration therapy), decreasing need for intravenous rehydration, vomiting, and failure of ORT.[13,15,17] Applicability to the Canadian context may be limited, as these three RCTs were conducted in developing countries. In one RCT in which children with dehydration were excluded, ondansetron was not found to be effective.[14] In the RCT in which level of dehydration was not described, ondansetron was not superior to placebo for reduction of vomiting.[16] A non-randomized study among children with mild to moderate dehydration secondary to gastroenteritis found no difference in returns and readmissions to the emergency department within 72 hours, for patients receiving ondansetron compared to those who did not.[18]

A systematic review published in 2016 was not included in this report due to an inability to determine eligibility of the comparison group.[21] Ten RCTs, including one of the RCTs included in this report,[17] were included in the systematic review and meta-analysis. Ondansetron was found to reduce risk of failure of oral rehydration therapy, risk of hospitalization, and need for intravenous rehydration as compared to placebo in children with vomiting and acute gastroenteritis. Additionally, a Cochrane review published in 2012 found clear evidence to support effectiveness of ondansetron in children with acute gastroenteritis and mild to moderate dehydration. As compared to placebo, ondansetron

reduced vomiting, need for intravenous rehydration, and hospitalization.[6] Evidence supporting the effectiveness of other antiemetics in children with acute gastroenteritis is lacking.[5,6] The findings of these systematic reviews and this report are in line with Canadian Pediatric Society recommendations to consider ondansetron in children presenting to the emergency department with vomiting related to suspected acute gastroenteritis and mild to moderate dehydration.[9] This recommendation is also consistent with the relative lack of evidence supporting effectiveness of ondansetron in children at risk of but not meeting for mild dehydration.

A nurse-initiated protocol for ondansetron and ORT in children with mild to moderate dehydration presenting to an emergency department was associated with earlier use of ondansetron and ORT and decreased intravenous fluid use in a before and after study of 128 patients.[22] Similarly, a clinical pathway including ondansetron and oral rehydration therapy implemented at an Emergency Department in Seattle was associated with decreased intravenous fluid use and decreased length of stay in a before and after study of 30519 patients.[23]

In summary, in pediatric patients with mild to moderate dehydration secondary to gastroenteritis, ondansetron is likely effective for decreasing risk of requiring intravenous rehydration and reducing vomiting as compared to placebo, both in combination with oral rehydration solution. The evidence does not support the effectiveness of ondansetron in children at risk of dehydration. Interpretation of these findings is limited by inconsistent outcome definitions, inconsistent methods of assessment of the presence and severity of dehydration, and applicability to the Canadian context.

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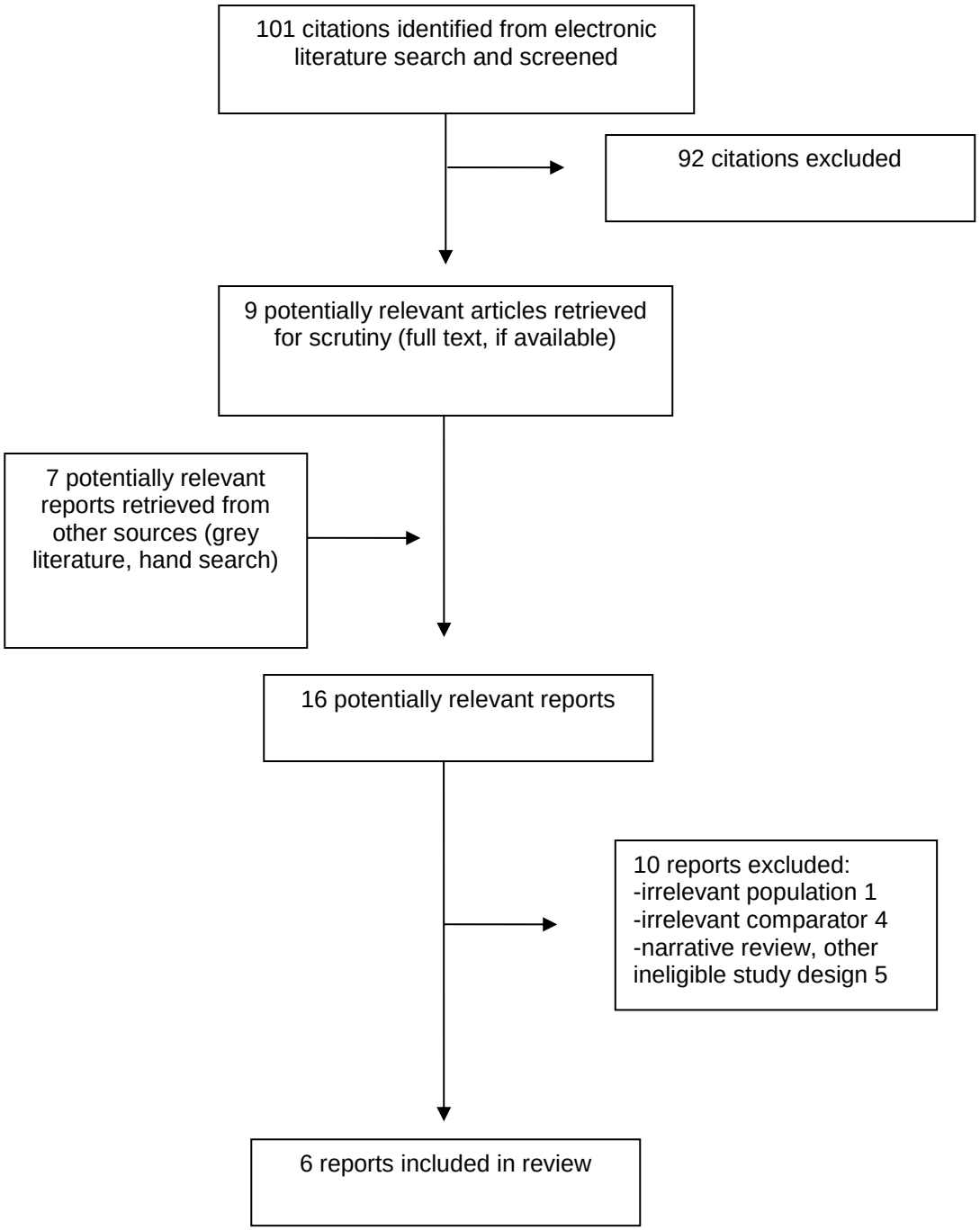
Appendix 1: Selection of Included Studies



Appendix 2: Study Characteristics

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trials				
Freedman, 2019 Pakistan[13]	RCT parallel-group, double-blind, placebo-controlled	Inclusion criteria: -Age 0.5 to 5 years old presenting to ED with acute gastroenteritis and dehydration -≥ 1 episode of vomiting and ≥ 1 episode of diarrhea within past 4 hours -"Some" dehydration according to WHO dehydration tool (severe dehydration excluded) -Median age: 18 months (both groups) -Median Clinical dehydration scale score: 2 (both groups) -58.7% male (ondansetron) and 61.2% male (placebo)	Intervention: Ondansetron ODT (2mg for weight 8-15kg; 4mg for 15kg and up) and weight-based ORT protocol using ORS Comparator: Placebo and weight-based ORT protocol using ORS	Primary outcome: intravenous rehydration (administration of ≥20 mL/kg over 4h of an isotonic fluid for the purpose of rehydration within 72h) Secondary outcomes: -presence and frequency of vomiting during within 4h -hospitalization for ≥24h -volume of ORS consumed within 4h -presence of some dehydration within 72h -number of diarrheal (i.e., loose or liquid) stools within 72h -treatment failure (intravenous rehydration, nasogastric rehydration for ≥24h, or death) within 72h
Freedman, 2019 Pakistan[14]	RCT parallel-group, double-blind, placebo-controlled	Inclusion criteria: -Age 0.5 to 5 years old presenting to ED with acute gastroenteritis and no dehydration -≥ 1 episode of vomiting and ≥ 1 episode of diarrhea within past 4 hours -Median age: 15 months (ondansetron), -16 months (placebo) 60.6% male (ondansetron), 58.3% male (placebo)	Intervention: Ondansetron ODT (2mg for weight 8-15kg; 4mg for 15kg and up) and weight-based ORT protocol using ORS Comparator: Placebo and weight-based ORT protocol using ORS	Primary outcome: intravenous rehydration (administration of ≥20 mL/kg over 4h of an isotonic fluid for the purpose of rehydration within 72h) Secondary outcomes: -presence and frequency of vomiting during within 4h -hospitalization for ≥24h -volume of ORS consumed within 4h -presence of some dehydration within 72h -number of diarrheal (i.e., loose or liquid) stools within 72h -treatment failure (intravenous rehydration, nasogastric rehydration for ≥24h, or death)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				within 72h
Rang, 2019[15] Vietnam	RCT parallel-group, double-blind, placebo-controlled	Inclusion criteria: -Age 11-60 months admitted to a Vietnam hospital pediatric ward with acute diarrhea (>3 stools in 24h), and mild to moderate dehydration -no blood in stool -no antiemetics given Children with severe gastroenteritis requiring IV rehydration were excluded -Median age: 14 (ondansetron) and 17 (placebo) -87% mild dehydration and 13% moderate dehydration (both groups) -67% male (ondansetron) and 45% male (placebo)	Intervention: Ondansetron 0.2mg/kg IV (maximum 8mg) once Comparator: Placebo (0.9% saline solution) IV once Both groups were also given 0.5mL/kg ORS every 2 minutes with a spoon, glass or cup. A physician re-evaluated the level of dehydration and the amount of ORS consumed every 4 hours. Rehydration was considered adequate once ≥40 mL/kg of ORS solution had been given	Primary outcome: Need for IV rehydration Secondary outcomes: -cessation of vomiting after 4h -number of vomiting episodes at 4, 8 and 24h -volume (per kg) of oral rehydration solution intake at 4 and 24h -number of diarrhea episodes -duration of diarrhea -length of hospital stay -adverse effects of ondansetron
Hagbom, 2017[16] Sweden	RCT parallel-group, double-blind, placebo-controlled	Inclusion criteria: -Age 6 months to 16 years presenting to ED with vomiting (within the past 4 hours) and diarrhea -confirmed norovirus or rotavirus infection Severe dehydration excluded -Mean age: 29 months (both groups) -52% female (ondansetron) and 56% female (placebo) -Rotavirus: 83% (both groups) -Norovirus: 17.5% (ondansetron and 9.8% (placebo)	Intervention: Oral ondansetron solution 0.15mg/kg Comparator: Identical oral placebo solution ORS was initiated 15 min after ondansetron or placebo in accordance with WHO recommendations	Final follow-up at 7-10 days Primary outcome: Number of vomiting and diarrhea episodes at 24h Secondary outcomes: -number of days with diarrhea and/or vomiting (secondary outcomes introduced starting with the 21st participant)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		-Both norovirus and rotavirus: 0% (ondansetron) and 7.3% (placebo)		
Danewa, 2016[17] India	RCT parallel-group, double-blind, placebo-controlled	Inclusion criteria: -Age 3 months to 5 years, presenting to pediatric ED with acute diarrhea and some dehydration (WHO criteria) -at least 2 reported episodes of vomiting within past 6 hours Mean age 15.5 months and 15.0 months 63.5% male (ondansetron) and 52.9% male (placebo) Dehydration score 12.5 (ondansetron) and 13.1 (placebo)	Intervention: Ondansetron oral liquid 0.2mg/kg Or Comparator: placebo Once prior to ORS Repeated once if vomiting within 30 minutes of first dose . In both groups: ORS at the rate of 75 mL/kg in first 4h. Repeat course of 75 mL/kg of ORS over 4h was given to children who continued to have features of some dehydration after initial 4h of therapy.	The primary outcomes: were failure of ORT (features of some dehydration persisting after 4h of ORT or severe dehydration at any time during assessment), administration of unscheduled intravenous fluids, and amount of ORS intake in 4h. Secondary outcomes: duration of dehydration correction, number of vomiting episodes in 4h, adverse effects, and caregiver satisfaction.
Non-randomized studies				
McLaren, 2019[18] United States	Comparative Cohort Study Retrospective	Inclusion criteria: -Age 6 months to 18 years -Presented to ED with vomiting due to gastroenteritis Median age 3.1 years (no ondansetron) vs 4.3 years (ondansetron) 52.2% male (no ondansetron) vs 51.5% male (ondansetron) Median dehydration score 1 (no	Intervention: Ondansetron, ondansetron administration in the ED Comparator: No ondansetron prescription, no ondansetron administration in the ED Oral rehydration therapy offered in 5-10mL aliquots, and advanced every 3 to 5	Unscheduled ED visit within 72h of discharge from ED

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		ondansetron) vs 2 (ondansetron)	minutes as tolerated	

ED = emergency department; IV = intravenous; ODT = oral disintegrating tablet; ORS = oral rehydration solution; ORT = oral rehydration therapy; RCT = randomized controlled trial

Appendix 3: Critical Appraisal

Table 3: Strengths and Limitations of Clinical Studies using RoB2[10] and ROBINS-I[11]

Strengths	Limitations
Randomized Controlled Trials	
Freedman, 2019[13]	
Randomization and allocation concealment well-described Physicians, research officers, patients and families, and on-site pharmacists blinded to treatment assignment Intention to treat analysis Protocol registered No loss to follow-up for primary outcome assessment	Conducted in Pakistan – may limit applicability to Canadian context
Freedman, 2019[14]	
Randomization and allocation concealment well-described Patients, treating physicians, investigators, and data assessors blinded to treatment assignment Intention to treat analysis Protocol registered No loss to follow-up	Conducted in Pakistan – may limit applicability to Canadian context Observed event rate was lower than anticipated (reduced power)
Rang, 2019[15]	
Randomization and allocation concealment well-described Only one participant lost to follow-up	Conducted in a hospital pediatric ward in Vietnam – may limit applicability to Canadian context Noted to be double-blind, but not clear who was blinded No description of protocol registration or pre-specified methods Statistical analysis did not account for multiple outcome measures
Hagbom, 2017[16]	
Randomized, allocation concealed Protocol registered Only three participants lost to follow-up	Conducted in Sweden – may limit applicability to the Canadian context Noted to be double-blind, but not clear who was blinded Statistical analysis did not account for multiple outcome measures Randomization and allocation concealment described in less detail Level of dehydration at baseline not provided Target enrollment not achieved
Danewa, 2016[17]	

Strengths	Limitations
Randomized, allocation concealed Blinding described Protocol registered Only three participants lost to follow-up	Conducted in India – may limit applicability to the Canadian context Statistical analysis did not account for multiple outcome measures
Non-randomized studies	
McLaren, 2019[18]	
Large sample size Clear inclusion and exclusion criteria Blinded outcome analysis	Non-randomized, retrospective Critical risk of bias due to confounding Intervention and comparison (with respect to oral rehydration therapy) was not well-described, and adherence to interventions not known Statistical methods not clearly defined a priori No description of protocol registration or pre-specified methods

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trials	
Freedman, 2019[13]	
Reported as % (n) or median (IQR) **Primary outcome – need for intravenous rehydration (ondansetron vs placebo)** 14.7% (68 of 462) vs 19.5% (89 of 456); OR: 0.71, 95% CI, 0.50 to 1.00; ARR: 4.8%, 95% CI, 0.0% to 9.7% **Secondary outcomes (ondansetron vs placebo)** Vomiting (yes/no): 13.2% (61/462) vs 26.1% (119/456); OR: 0.43, 95% CI, 0.31 to 0.61; ARR: 12.9%, 95% CI: 7.8% to 18.0% Vomiting frequency: 0 (0-0) vs 0 (0-1) (p<0.001) Volume of oral fluids: 4.2 (2.2-6.6) mL/kg/h vs 3.8 2.1-6.0) mL/kg/h (p>0.99) Hospitalization: 6.3% (29/462) vs 7.2% (33/456); OR 0.86, 95% CI 0.52-1.45 Presence of dehydration: 27.1% (125/462) vs 26.3% (120/456); OR 1.04, 95% CI 0.78 to 1.40 Diarrhea frequency: 4 (0-7) vs 3 (0-6) (p>0.99) Treatment failure: 14.7% (68/462) vs 19.5% (89/456) (p=0.37) **Adverse events:** No serious adverse events Similar between groups overall	"Among children with gastroenteritis-associated vomiting and dehydration, oral ondansetron administration reduces vomiting and intravenous rehydration use. These findings should be replicated in a larger multicenter trial, and if successful, ondansetron use should be considered to promote ORT success among dehydrated children in LMICs."(pg.9)
Freedman, 2019[14]	
Primary outcome – need for intravenous rehydration (ondansetron vs placebo) 10.3% (32/312) vs 10.8% (38/314); OR 0.95, 95% CI 0.56 to 1.59	"In summary, our findings do not provide evidence to support the routine administration of a single dose of oral ondansetron for the prevention of intravenous fluid administration in

Main Study Findings	Authors' Conclusion
Secondary outcomes (ondansetron vs placebo) Vomiting (yes/no): 19.6% (61/312) vs 24.0% (75/314); OR 0.77, 95% CI 0.53 to 1.13 Median number of vomiting episodes: 0 (0 to 0) vs 0 (0 to 0) Volume of oral fluids consumed (mL/kg/h): 3.4 (1.9 to 5.7) vs 3.2 (1.9 to 5.9) Hospitalization: 3.8% (12/312) vs 3.5% (11/314) OR 1.11, 95% CI 0.48 to 2.55 Presence of dehydration: 5.8% (18/312) vs 7.6% (24/314) OR 0.74, 95% CI 0.39 to 1.39 Diarrhea Frequency: Median 4 (1 to 7) vs 4 (1 to 6) Treatment failure: 10.3% (32/312) vs 10.8% (38/314); OR 0.95, 95% CI 0.56 to 1.59 **Adverse events:** No serious adverse events Similar between groups overall	children with gastroenteritis but without evidence of dehydration."(pg.264)
Rang, 2019[15]	
Primary outcome (ondansetron vs placebo) Need for intravenous rehydration: 10% (3/30) vs 39% (12/31); RR 0.51, 95% CI 0.33 to 0.79 (P=0.003) **Secondary outcomes (ondansetron vs placebo)** Complete cessation of vomiting: 73% (22/30) vs 23% (7/31) Number of episodes of vomiting (median): at 4h (0 vs 1, P<0.001), 8h (0 vs 1, P<0.001) and 24h (1 vs 3, P<0.001) ORS consumption (median): at 4h (250mL vs. 190 mL, P<0.001) and 24 h (450 mL vs. 350mL, P=0.019) Number of diarrhea episodes (median): 5 vs. 6, P=0.913 Duration of diarrhea (median): 66h vs. 72h, P=0.632 Length of hospital stay (median): 4d vs 4d, P=0.828	"In summary, single dose of intravenous ondansetron seems to be effective for the cessation of episodes of emesis and in lowering the rates of IV rehydration, without affecting the duration of diarrhea and hospital stay, in hospitalized patients with gastroenteritis associated with emesis."(pg.470)
Hagbom, 2017[16]	
Primary outcomes (ondansetron vs placebo, n=81): Number of vomiting episodes at 24h: median 0.0 ±2.0 IQR vs. 0.0 ±2.0 (P=0.988**)** Number of diarrhea episodes at 24h: median 1.0 ±5.0 IQR vs. 3.5 ±9.0 (P=0.063) **Secondary outcomes (ondansetron vs placebo, n=64):** Days with symptoms: median 4.0 ±3.0 IQR vs. 6.0 ±4.0 (P=0.031) **Adverse events:** 1 serious adverse event with ondansetron and 2 with placebo, deemed to be unlikely due to study drug	"Ondansetron may be a beneficial treatment for children with rotavirus gastroenteritis."(pg.1)
Danewa, 2016[17]	
Primary outcomes (ondansetron vs placebo): Failure of ORT: 31% (26/84) vs 61.5% (51/83); RR 0.50 (95% CI 0.35-0.72), P < .001, ARR 30%. Administration of unscheduled intravenous fluid: 14.3% (12/84) vs 25.3% (21/83); RR 0.56 (0.30, 1.07), p=0.074 Amount of ORS intake in 4h (mean): 645mL vs 554mL, mean difference 91.3mL (95% CI 35.0 to 147.6), p=0.002 **Secondary outcomes:**	"Our results favored the use of ondansetron to overcome the barrier of vomiting in successful implication of ORT therapy by reducing the proportion of children who failed ORT. However, one needs to study the metrics around failure of ORT other than vomiting and decision to administer ondansetron."(pg. 108)

Main Study Findings	Authors' Conclusion
Duration of dehydration correction (median): 4h vs 6h, P < .001 Number of vomiting episodes in 4h (mean): 1.8 vs 3.6, mean difference -1.8 (95% CI -2.6 to -1.1), p<0.001 Adverse effects: None in either group Caregiver satisfaction: Statistically significantly improved in all fields (mood, activity, alertness, comfort, number of vomiting episodes, fluid intake) was statistically significantly improved with ondansetron	
Non-randomized Study	
McLaren, 2019[18]	
Primary outcome - Return to emergency department within 72 hours (n=11,785) **Ondansetron prescription vs no ondansetron prescription on ED discharge:** Adjusted OR 1.31 (95% CI 1.09 to 1.58) (Adjusted for ESI, age, insurance source, race, time of index visit registration) Adjusted OR 1.12 (95% CI 0.92 to 1.33) (Adjusted for ESI, age, insurance source, race, time of index visit registration, and receipt of ondansetron in the emergency department) **Ondansetron administration vs no ondansetron administration in the ED:** **OR 1.64 (95% CI 1.32 to 2.04)** (Adjusted for ESI, age, insurance source, race, time of index visit registration) **OR 1.13 (95% CI 0.63 to 2.02)** (Subgroup of patients with dehydration scores)	"There was no association between ondansetron prescription and ED revisit among children seen in the ED with suspected acute gastroenteritis. In the appropriate setting, however, physicians may consider prescribing ondansetron for symptom control in conjunction with careful discharge instructions" (pg. 1)

ARR = absolute risk reduction; CI = confidence interval; ED = emergency department; ESI = emergency severity index; IQR = interquartile range; LMIC = low- and middle-income countries; OR = odds ratio; ORT = oral rehydration therapy; RR = relative risk

Appendix 5: Additional References of Potential Interest

Studies evaluating relevant protocols or pathways

Hendrickson MA, Zaremba J, Wey AR, Gaillard PR, Kharbanda AB. The Use of a Triage-Based Protocol for Oral Rehydration in a Pediatric Emergency Department. Pediatr Emerg Care. 2018;34(4):227-232.

Rutman L, Klein EJ, Brown JC. Clinical Pathway Produces Sustained Improvement in Acute Gastroenteritis Care. Pediatrics. 2017;140(4).

Potentially relevant systematic reviews that did not meet eligibility criteria

Tomasik E, Ziolkowska E, Kolodziej M, Szajewska H. Systematic review with meta-analysis: ondansetron for vomiting in children with acute gastroenteritis. Aliment Pharmacol Ther. 2016;44(5):438-446.

Carter B, Fedorowicz Z. Antiemetic treatment for acute gastroenteritis in children: an updated Cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. BMJ Open. 2012;2(4).