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Oral Rehydration Solutions versus Drink of Choice in Children with Dehydration: A Review of Clinical Effectiveness

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Abbreviations

RCT	randomized controlled trial

Context and Policy Issues

Children generally have a higher body water content (60-75%) compared to adults (55-60%).[1] Dehydration in children is a concern as their higher body water content makes them more prone to water, sodium and potassium loss during acute illnesses.[1] Vomiting, diarrhea, or other causes of excessive fluid loss can lead to varying degrees of dehydration from mild (3-5% weight loss) to moderate (6-10% weight loss) and severe (10-15% weight loss).[1] Symptoms of dehydration in children differ according to the degree of dehydration, but can include hyperirritability, lethargy, intense thirst, mottled or cyanotic skin, a rapid pulse, hypotension and shock in more severe cases.[1]

Three types of dehydration can occur: isonatremic, hypernatremic, and hyponatremic.[1] Isonatremic dehydration is the most common presentation (80% of cases) and is characterized by equal loss of water and salt.[1] Hypernatremic dehydration represents a smaller fraction of cases (15%) and is characterized by a greater water loss.[1] Hyponatremic dehydration is the rarest presentation (5% of cases) and is characterized by either excessive water intake, sodium depletion or an artificial lowering of serum sodium concentration secondary to an increase in glucose, electrolytes, lipids and proteins.[1] The treatments of the different types of dehydration vary, but all involve replacing fluid deficits.[1]

Oral rehydration therapy is the first line treatment for children with mild to moderate dehydration.[1] Commercially available oral rehydration solutions contain specific concentrations of sodium, potassium and glucose with the aim of optimizing fluid absorption through the gastrointestinal tract via the sodium-glucose cotransporter pump.[1,2] Oral rehydration solutions can thus be used for all types of dehydration as long as the serum sodium concentrations are not at the extreme ends of the spectrum in hyponatremic or hypernatremic dehydration.[1] However, oral rehydration solutions are considered to be prohibitively expensive for some patients (or their guardians) and often have an unpleasant taste.[3] This may lead to dehydrated children being treated with other beverages which may not contain the optimal carbohydrate and electrolyte concentrations needed for rehydration.[3] Other, often more palatable, oral rehydration options include water, clear broths, ice pops, and juice or sports drinks.[4]

This report aims to summarize the evidence regarding the comparative clinical effectiveness of oral rehydration solution versus other fluids of choice for pediatric patients with, or at risk of, dehydration.

Research Question

What is the comparative clinical effectiveness of oral rehydration solution versus other fluids of choice for pediatric patients with, or at risk of, dehydration?

Key Findings

One relevant randomized controlled trial was identified regarding the clinical effectiveness of half-strength apple juice followed by preferred fluids versus a commercially available electrolyte maintenance solution in pediatric patients with minimal dehydration secondary to

gastroenteritis. Overall, half-strength apple juice followed by preferred fluids were found to be both non-inferior and superior to the electrolyte maintenance solution in the primary composite outcome of overall treatment failure. However, the results of this trial should be interpreted with caution as several limitations were identified. The authors of the trial concluded that dilute apple juice followed by preferred fluids may be an alternative to electrolyte maintenance solutions.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, 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 rehydration solutions, oral administration and pediatrics. No search filters were applied to limit retrieval by publication 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 30, 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 under 18 years with, or at risk of, mild to moderate dehydration from any cause
Interventions	Oral rehydration solutions (e.g., electrolyte solutions, Pedialyte)
Comparators	Drink of choice, preferred beverages, juices, water, milk
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, hyponatremia)
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 randomized controlled trial (RCT) was critically appraised by one reviewer using the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist 2.[5] Summary scores were not calculated for the included study; rather, a review of the strengths and limitations of the included study was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 322 citations were identified in the literature search. Following screening of titles and abstracts, 315 citations were excluded and seven potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, seven publications were excluded for various reasons, and one publication, an RCT,[3] met the inclusion criteria and was included in this report. Appendix 1 represents the PRISMA[6] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Detailed characteristics of the included publication are provided in Appendix 2.

Study Design

The RCT[3] was a single center, randomized, single-blind, non-inferiority trial published in 2016. The trial aimed to determine if half-strength apple juice (i.e., a commercial brand apple juice diluted with sterile water in a 1 to 1 ratio) followed by preferred fluids were non-inferior to (i.e., not worse than) a commercially available electrolyte maintenance solution in the treatment of children with minimal dehydration secondary to gastroenteritis.[3] In this case, if the upper bound of the 95% confidence interval (CI) for the primary outcome was less than the non-inferiority margin of +7.5%, inferiority was rejected.[3] If non-inferiority of the intervention to the comparator was confirmed, the authors planned to subsequently test for superiority.

Country of Origin

The RCT[3] was conducted in Canada.

Patient Population

The RCT[3] was conducted in the emergency department of a tertiary care hospital in Toronto, Ontario, Canada and included 647 pediatric patients 6 to 60 months of age with minimal dehydration secondary to gastroenteritis. Patients were eligible for inclusion in the trial if they had three or more episodes of vomiting or diarrhea in the preceding 24 hours and symptom onset within the preceding 96 hours, weighed eight or more kilograms, had a Clinical Dehydration Scale score <5, and a capillary refill time <2 seconds.[3] All patients also had to be residents of Ontario for inclusion into the trial.[3]

Interventions and Comparators

In the RCT,[3] the intervention was half-strength apple juice (i.e., Fairlee commercial brand apple juice diluted with sterile water in a 1 to 1 ratio) followed by preferred fluids which was tested for non-inferiority and superiority compared to an apple flavored, sucralose sweetened electrolyte maintenance solution (Life Brand manufactured by Pharmascience for Shoppers Drug Mart). While in hospital, patients received 5 mL of their assigned fluid every 2 to 5 minutes.[3] This consisted of only the half-strength apple juice portion of the intervention or the electrolyte maintenance solution of the comparator.[3] Treatment crossover was permitted if the treating physician deemed consumption or hydration status to be unsatisfactory.[3] After discharge from the emergency room, fluids were replaced at a

prescribed rate of 2 mL/kg per vomiting episode and 10 mL/kg per diarrheal episode.[3] Patients in the intervention arm were then permitted to replace fluids with their beverage of choice (other than electrolyte maintenance solutions) and to resume their normal diet as soon as possible.[3] Patients in the comparator arm replaced fluids with commercially available electrolyte maintenance solutions (Pedialyte, Enfalyte, Gastrolyte, etc.) and were permitted to resume a normal diet as soon as tolerable.[3] If the patients in the comparator arm vomited, they were instructed to replace fluids with the electrolyte maintenance solution only for four hours before resuming a normal diet again.[3]

Outcomes

In the RCT,[3] the primary outcome was treatment failure defined by any of the following occurring within 7 days of patient enrollment: patient hospitalization or intravenous rehydration, subsequent unscheduled physician encounter for the same episode of vomiting or diarrhea, protracted symptoms occurring >7 days after enrollment, physician request to administer crossover solution at initial visit, or ≥3% weight loss or Clinical Dehydration Scale score of ≥5 at in person follow-up.[3] The Clinical Dehydration Scale is a 4-item, 8-point scale used to estimate the degree of dehydration in children with gastroenteritis; the higher the score, the more severe the degree of dehydration.[3] A score of 0 to 4 is considered mild dehydration and a score of 5 to 8 is considered moderate to severe dehydration.[3] Secondary outcomes of interest were incidence of need for intravenous rehydration at initial visit (i.e., after patients were randomized to their groups and were treated with their assigned oral intervention, the treating physician judged oral consumption or hydration status to be unsatisfactory and prescribed intravenous rehydration) or at subsequent visit within 7 days of patient enrollment, incidence of patient hospitalization at initial visit (i.e., oral treatment failure resulting in physician admitting the patient into the hospital) or a subsequent visit, frequency of diarrhea and vomiting, and the percentage weight change at the 72 to 84 hour reassessment.

Summary of Critical Appraisal

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

The RCT[3] had several strengths including a clear research question, relevant population eligibility criteria, and an appropriate choice of active control as per the treatment recommendations from the Canadian Pediatric Society and the American Academy of Pediatrics/Centers for Disease Control. Participants were appropriately randomized, investigators were blinded to randomization assignment and allocation concealment was extensively described.[3] The randomization table was stored with pharmacy staff who were not involved in patient selection, enrollment or treatment allocation.[3] This also reduced the likelihood of investigators being unblinded. The trial had an *a priori* protocol and was also registered (NCT01185054).[3] The prespecified sample size was met as 647 patients were included in the trial compared to the calculated 624 participants needed to yield an 80% power to reject the null hypothesis.[3] The non-inferiority margin (i.e., the boundary for which the effect of the intervention was considered not worse than the comparator) was appropriately determined *a priori* through a focus group discussion with experts in the field, and the plan and criteria to test for superiority were described before the start of the trial.[3] The trial utilized an intention-to-treat analysis and had extensive follow-up methods which led to minimal data lost to follow-up (i.e., data from only three patients were unaccounted for).[3] Finally, the authors declared the sources of funding for the trial and reported that they had no conflicts of interest.[3]

The trial's[3] main limitation was that the patients and their guardians were unblinded when they left the emergency department so they could continue the correct intervention at home. As some of the outcomes were subjective (e.g., unscheduled health care visits, which were based on a decision by the patients' guardians), there was the possibility that being aware of the treatment assignment may have influenced the guardians' decisions to seek additional health care which decreases the certainty of the results. However, it would have been difficult and unfeasible to control for this without considerably limiting the generalizability of the study. The prescribed rehydration regimens used were those recommended by the Centers for Disease Control and Prevention for managing acute gastroenteritis among children, however, the volume of fluid consumed and patient adherence were not measured.[3] It was unclear if different volumes of fluid at home, or differences in fluid composition, led to the observed results. Furthermore, although baseline characteristics of the groups appeared to be similar and the authors reported no differences between groups, no statistical testing or description of what would represent clinically meaningful differences was provided.[3] Lastly, the RCT[3] was conducted at a tertiary care pediatric hospital in Toronto, Ontario, and the participants were restricted to residents of Ontario. As Canadian patients in remote areas may not have access to the resources of a hospital (e.g., a physician to prescribe ondansetron which was administered to 67.4% of patients in this trial to decrease the need for intravenous rehydration), the results may not be generalizable to the full Canadian setting.

Summary of Findings

One RCT[3] relevant to this report was identified. Appendix 4 Table 4 presents the main study findings and the authors' conclusions.

Clinical Effectiveness of Oral Rehydration Solutions

Overall Treatment Failure (Primary Composite Outcome)

The RCT[3] relevant to this report tested half-strength apple juice followed by preferred fluids for non-inferiority (non-inferiority margin of +7.5%) and superiority (*a priori* plan to test for superiority if non-inferiority established) versus an electrolyte maintenance solution for the primary composite outcome of treatment failure within seven days of patient enrollment. Overall, patients who were administered half-strength apple juice followed by preferred fluids experienced treatment failure statistically significantly less often than patients administered the electrolyte maintenance solution (97.5% CI, -∞ to -2.0, $P < 0.001$ for non-inferiority and $P = 0.006$ for superiority).[3] In terms of the individual components of the composite outcome, there was a significantly lower incidence of the need for intravenous rehydration (both the initial visit and follow-up visit combined) in those who were administered half-strength apple juice followed by preferred fluids compared to those who were administered the electrolyte maintenance solution (99% CI, -11.6 to -1.8, $P = 0.001$).[3] However, there were no statistically significant differences between the two groups in the incidence of subsequent unscheduled health care visits for the same episode of vomiting/diarrhea (99% CI, -10.5 to 3.8, $P = 0.26$), incidence of weight loss or dehydration at follow-up visit (99% CI, -33.8 to 50.9, $P = 0.99$), incidence of hospitalization (99% CI, -5.4 to 1.3, $P = 0.14$), incidence of extended symptomatology (99% CI, -1.9 to 5.6, $P = 0.26$) or incidence of physician request for treatment allocation crossover (99% CI, -5.7 to 0.8, $P = 0.06$).[3]

Incidences of Intravenous Rehydration Therapy (Secondary Outcome)

The RCT[3] found that there was a significantly lower incidence of the need for intravenous rehydration therapy following treatment at the initial emergency department visit in those who were administered half-strength apple juice compared to those who were administered the electrolyte maintenance solution (99% CI, -10.5 to -2.0, *P* = 0.001). No significant difference was found between the two groups during follow-up within 7 days of initial visit (99% CI, -5.4 to 2.1, *P* = 0.33).[3]

Incidences of Hospitalization (Secondary Outcome)

The RCT[3] found that there was no statistically significant difference between groups in hospitalizations following treatment (i.e., with half-strength apple juice followed by preferred fluids or electrolyte maintenance solution) at the initial emergency department visit (99% CI, -4.7 to 1.0, *P* = 0.12) or at follow-up within 7 days of initial visit (99% CI, -3.7 to 2.3, *P* = 0.73).

Frequency of Vomiting and Diarrhea Episodes (Secondary Outcome)

The RCT[3] found that there was no statistically significant difference between those who were administered half-strength apple juice followed by preferred fluids compared to those who were administered the electrolyte maintenance solution in the frequency of vomiting (99% CI, 0.77 to 1.49, *P* = 0.39) or diarrhea episodes (99% CI, 0.79 to 1.64, *P* = 0.60).

Median Percentage Weight Change (Secondary Outcome)

The RCT[3] found that there was no statistically significant difference between those who were administered half-strength apple juice followed by preferred fluids compared to those who were administered the electrolyte maintenance solution in median percentage weight change at reassessment (*P* = 0.18).

Limitations

There were several limitations to this report, one of which was the small amount of relevant literature; only one RCT[3] relevant to this report was identified. Studies not meeting the inclusion criteria of this report often compared oral rehydration solutions to different oral rehydration solutions or to intravenous rehydration therapy. This suggests the need for more research comparing the effectiveness of oral rehydration solutions to beverages of choice in children.

The evidence in this report was also limited by the generalizability of the interventions and comparator used in the included RCT.[3] Data were not provided regarding the amounts of fluids consumed in either group.[3] Therefore, it is not possible to determine whether the quantity of fluids consumed, or the particular composition of the fluids, contributed to the observed results.

Lastly, the authors of the included RCT discussed the uncertain generalizability of their trial because of the use of a specific commercial electrolyte maintenance solution in the comparator arm.[3] However, patients in the intervention arm were administered half-strength apple juice in the emergency department and then allowed to choose their preferred beverage for rehydration once discharged home.[3] The different possible preferred fluids (e.g., apple juice, orange juice, grape juice, milk, sports drinks) do not have the same carbohydrate, electrolyte or osmolarity compositions.[3] Although it was not the objective of the study to determine the optimal rehydration solution, this may be a reasonable future

direction as there was uncertainty around whether differences between groups in volume and/or composition of fluids contributed to the observed results.

Conclusions and Implications for Decision or Policy Making

This report identified one RCT[3] (a single center, randomized, single-blind, non-inferiority trial) which aimed to determine if half-strength apple juice followed by preferred fluids was non-inferior to a standard electrolyte maintenance solution in children with minimal dehydration secondary to gastroenteritis. A statistically significant difference in the primary composite outcome of overall treatment failure was attained in the tests for both non-inferiority and superiority, suggesting that half-strength apple juice followed by preferred fluids was not inferior to a standard electrolyte maintenance solution, and may be superior to this commercially available product.[3] In terms of the components of the primary composite outcome, only one was significantly different between the treatment groups (i.e., incidence of intravenous rehydration) whereas there were no statistically significant differences with the five other components (i.e., subsequent unscheduled health care visits for the same episode of vomiting/diarrhea, incidence of weight loss or dehydration at follow-up visit, incidence of hospitalization, incidence of extended symptomatology and incidence of physician request for treatment allocation crossover).[3]

Overall, the findings from the RCT[3] included in this report come with a degree of uncertainty and the limitations discussed should be considered when interpreting the results. The limited quantity of evidence suggests the need for well-designed RCTs to investigate the comparative clinical effectiveness of oral rehydration solutions versus other fluids of choice for pediatric patients with dehydration.

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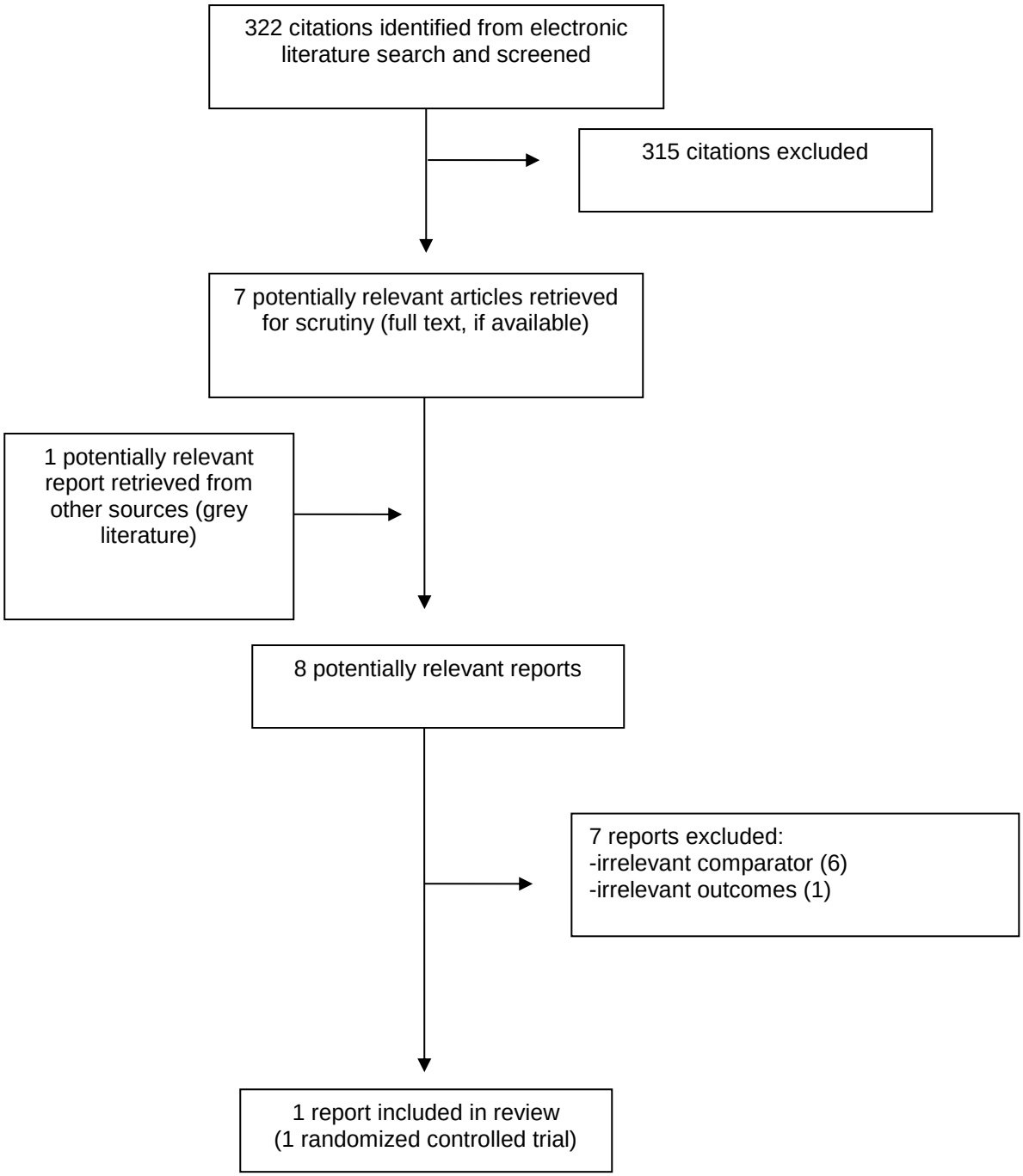
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Study

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator	Clinical Outcomes, Length of Follow-Up
Freedman, 2016[3] **Canada** **Funding:** Physician Services Incorporated Foundation (grant 10q1011)	**Study design:** Single center, randomized, single-blind, non-inferiority trial (n= 647). **Setting:** Emergency department of a tertiary care pediatric hospital in Toronto, Ontario, Canada. **Purpose:** To determine if fluids as tolerated is non-inferior to standard electrolyte maintenance solutions in children with minimal dehydration.	Children aged 6 to 60 months with minimal dehydration secondary to gastroenteritis. **Inclusion criteria:** • Three or more episodes of vomiting or diarrhea in preceding 24 hours • Symptom onset within preceding 96 hours • Weight ≥8 kilograms • Minimal dehydration (score 0-4) as defined by an 8-point Clinical Dehydration Scale[a] • Capillary refill <2 seconds • Ontario resident **Exclusion criteria:** • History of chronic gastrointestinal disease or other diseases which increase the risk of treatment failure • Prematurity with corrected postnatal age <30 weeks • History of bilious vomiting, hematemesis, hematochezia, or clinical concern for acute abdomen • Requirement for intravenous rehydration • Insurmountable language barrier **Number of patients in trial arms (intervention vs control):** 323 vs 324 **Mean age of patients (intervention vs control):** 28.0 months vs 29.0 months **Mean weight of patients (intervention vs control):** 14.9 kg vs 14.6 kg **Vomiting episodes in preceding 24 hours (intervention vs control):** 5 vs 5	**Intervention:** Half-strength apple juice (60 g/L carbohydrates, 0 mmol/L sodium, 22 mmol/L potassium, 22 mmol/l chloride, 365 mOsm/L osmolarity), followed by patient's preferred beverage once discharged home **Comparator:** Apple-flavored, sucralose sweetened electrolyte maintenance solution (25 g/L carbohydrates, 45 mmol/L sodium, 20 mmol/L potassium, 35 mmol/L chloride, 20 mmol/L base, 250 mOsm/L osmolarity) Patients received 5 mL of assigned fluid every 2 to 5 minutes while in hospital. Ondansetron was administered to all patients who vomited. Crossover permitted if physician deemed consumption or hydration status unsatisfactory. Post-discharge fluids were replaced at a rate of 2 mL/kg per vomiting episode and 10 mL/kg per diarrheal episode. Patients in the intervention arm were permitted to replace fluids with beverage of choice (other than electrolyte maintenance solutions) and to resume normal diet as	**Primary composite outcome:** • Incidence of treatment failure (defined as any of the following occurring within 7 days of enrollment: hospitalization or intravenous rehydration, subsequent unscheduled physician encounter for the same episode of vomiting or diarrhea, protracted symptoms occurring >7 days after enrollment, physician request to administer crossover solution at initial visit, ≥3% weight loss or Clinical Dehydration Scale score of ≥5 at in person follow-up). **Secondary outcomes:** • Incidence of need for intravenous rehydration at initial visit or subsequent visit within 7 days of enrollment • Incidence of hospitalization at initial visit or a subsequent visit • Frequency of diarrhea and vomiting • Percentage weight change at the 72 to 84 hour reassessment **Follow-up:** Daily phone call by research nurse until child was asymptomatic for 24 hours, caregiver diary returns at in-person reassessment or by mail, and/or provincial registries for hospital discharge diagnoses and

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator	Clinical Outcomes, Length of Follow-Up
		Diarrhea episodes in preceding 24 hours (intervention vs control): 3 vs 3 **Baseline Clinical Dehydration Scale[a] score distribution (intervention vs control)**: **0:** 67.8% vs 68.5% **1:** 13.0% vs 14.2% **2:** 12.1% vs 11.7% **3:** 2.5% vs 4.0% **4:** 4.6% vs 1.5% **Administration of ondansetron (intervention vs control):** 66.3% vs 68.5%	soon as possible. Patients in comparator arm replaced fluids with commercially available electrolyte maintenance solutions (Pedialyte, Enfalyte, Gastrolyte, etc.) and were permitted to resume a normal diet as soon as tolerable. If the patients in the comparator arm vomited, they were instructed to replace fluids with the electrolyte maintenance solution for only four hours before resuming a normal diet again.	emergency department visit diagnoses.

[a] The Clinical Dehydration Scale is a 4-item, 8-point scale used to estimate the degree of dehydration in children with gastroenteritis. The higher the score, the more severe the degree of dehydration. A score of 0 to 4 is considered mild dehydration whilst a score of 5 to 8 is considered moderate to severe dehydration.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using SIGN Methodology Checklist 2[5]

Strengths	Limitations
Freedman, 2016[3]	
• The study addressed an appropriate and clearly focused research question • The inclusion and exclusion criteria were well defined and appropriate considering the study population and the research question • The assignment of participants to the intervention and control arms were randomized (one to one ratio using computer generated blocks of eight) • Allocation concealment was well described (color-matched, refrigerated study solutions in opaque, identical appearing bottles) • Investigators were blinded to the intervention (physicians reported being unaware of the treatment assignment in 96.9% of cases) • The authors choice of active control was justified by treatment recommendations from the Canadian Pediatric	• Although blinded to the intervention while in hospital, participants and their guardians were told their treatment assignment at discharge to continue the correct intervention at home • Although baseline characteristics of the groups appeared to be similar and the authors reported no differences between groups, no statistical testing or description of what would represent clinically meaningful differences was provided • Although the prescribed rehydration regimens were appropriate (i.e., regimen recommended by the Centers for Disease Control and Prevention for managing acute gastroenteritis among children), there was uncertainty regarding the volume of fluid consumed and patient adherence once discharged home • The trial was conducted at a single center and was restricted to residents of Ontario

Society and the American Academy of Pediatrics/Centers for Disease Control • The non-inferiority margin (+7.5%) was determined a priori through a focus group discussion with experts in the field • A power calculation was included in which enrolling 624 participants yielded an 80% power to reject the null hypothesis (647 patients included in trial) • The trial utilized an intention-to-treat analysis • The trial utilized various methods for follow-up which led to 99.5% (644 of 647 patients) of patients' data being collected • Drop-out rates were low as only one patient in the comparator group did not receive therapy and left the emergency department • The trial had an *a priori* protocol which included a plan to test for superiority if non-inferiority was confirmed. The trial was also registered (NCT01185054) • Funding source was declared (a Physician Services Incorporated Foundation grant), and they had no input in the design or conduct of the study • Authors disclosed conflicts of interest and none were reported	

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Freedman, 2016[3]	
As this trial tested non-inferiority of half-strength apple juice followed by preferred fluids compared to an electrolyte maintenance solution, between group differences were calculated as the proportion of the half-strength apple juice followed by preferred fluids group minus the proportion of the electrolyte maintenance solution group. **Overall treatment failure by any criteria[a] (primary composite outcome):** • Half-strength apple juice: 54/323 (16.7%) • Electrolyte maintenance solution: 81/324 (25.0%) • Between group difference of -8.3 (97.5% CI, -∞ to -2.0) (*P* < 0.001 for non-inferiority and *P* = 0.006 for superiority) **Components of primary outcome:** <u>Incidence of subsequent unscheduled health care visit for the same episode of vomiting/diarrhea:</u> • Half-strength apple juice/preferred fluids: 41/323 (12.7%) • Electrolyte maintenance solution: 52/324 (16.1%)	*"These results challenge the recommendation to routinely administer electrolyte maintenance solution when diarrhea beings."* (p. 1972) *"Among children with mild gastroenteritis and minimal dehydration, initial oral hydration with dilute apple juice followed by their preferred fluids, compared with electrolyte maintenance solution, resulted in fewer treatment failures. In many high-income countries, the use of dilute apple juice and preferred fluids may be an appropriate alternative to electrolyte maintenance solution use in children with mild gastroenteritis and minimal dehydration."* (p. 1973)

• Between group difference of -3.4 (99% CI, -10.5 to 3.8) (*P* = 0.26) Incidence of ≥3% weight loss or Clinical Dehydration Scale score of ≥5 at in person follow-up (20 children seen in scheduled follow-up): • Half-strength apple juice/preferred fluids: 2/10 (20.0%) • Electrolyte maintenance solution: 1/10 (10%) • Between group difference of +10.0 (99% CI, -33.8 to 50.9) (*P* = 0.99) Incidence of need for intravenous rehydration[b]: • Half-strength apple juice/preferred fluids: 8/323 (2.5%) • Electrolyte maintenance solution: 29/324 (9.0%) • Between group difference of -6.5 (99% CI, -11.6 to -1.8) (*P* = 0.001) Incidence of hospitalization[b]: • Half-strength apple juice/preferred fluids: 3/323 (0.9%) • Electrolyte maintenance solution/preferred fluids: 9/324 (2.8%) • Between group difference of -1.9 (99% CI, -5.4 to 1.3) (*P* = 0.14) Incidence of ≥3 episodes of vomiting/diarrhea within 24-hour period >7 days after enrollment (among those for whom diary or telephone follow-up was completed): • Half-strength apple juice/preferred fluids: 9/297 (3.0%) • Electrolyte maintenance solution: 4/294 (1.4%) • Between group difference of +1.7 (99% CI, -1.9 to 5.6) (*P* = 0.26) Incidence of physician request to administer a solution representing treatment allocation crossover: • Half-strength apple juice/preferred fluids: 2/323 (0.9%) • Electrolyte maintenance solution: 9/324 (2.8%) • Between group difference of -2.2 (99% CI, -5.7 to 0.8) (*P* = 0.06) **Secondary Outcomes:** Incidence of need for intravenous rehydration at initial emergency department visit: • Half-strength apple juice/preferred fluids: 3/323 (0.9%) • Electrolyte maintenance solution: 22/324 (6.8%) • Between group difference of -5.9 (99% CI, -10.5 to -2.0) (*P* < 0.001) Incidence of need for intravenous rehydration during follow-up within 7 days of initial visit: • Half-strength apple juice/preferred fluids: 6/323 (1.9%) • Electrolyte maintenance solution: 11/324 (3.4%) • Between group difference of -1.5 (99% CI, -5.4 to 2.1) (*P* = 0.33) Incidence of hospitalization at initial visit: • Half-strength apple juice/preferred fluids: 1/323 (0.3%)	

• Electrolyte maintenance solution: 6/324 (1.9%) • Between group difference of -1.5 (99% CI, -4.7 to 1.0) (*P* = 0.12) <u>Incidence of hospitalization at follow-up within 7 days of initial visit:</u> • Half-strength apple juice/preferred fluids: 3/323 (0.9%) • Electrolyte maintenance solution: 5/324 (1.5%) • Between group difference of -0.6 (99% CI, -3.7 to 2.3) (*P* = 0.73) <u>Frequency of diarrhea episodes (no numerical data provided), electrolyte maintenance solution: half-strength apple juice/preferred fluids:</u> Rate Ratio = 1.14 (99% CI, 0.79 to 1.64) (*P* = 0.60) <u>Frequency of vomiting episodes (no numerical data provided), electrolyte maintenance solution: half-strength apple juice/preferred fluids:</u> Rate Ratio = 1.07 (99% CI, 0.77 to 1.49) (*P* = 0.39) <u>Median percentage weight change at reassessment:</u> • Half-strength apple juice/preferred fluids: 0.00% (IQR, -0.55% to 0.37%) • Electrolyte maintenance solution: -1.19% (IQR, -3.58% to 0.43%) • Between group statistical comparison (*P* = 0.18)	

IQR = Interquartile range.

[a] If the upper bound of the 95% confidence interval for the primary outcome was less than the non-inferiority margin of +7.5%, inferiority was rejected.

[b] The overall sum for the incidence of the need for intravenous rehydration as a component of the primary outcome was less than the sum of the initial and follow-up incidences of the needs for intravenous rehydration as secondary outcomes because some children experienced the outcome at both the initial and follow-up visits (and were counted only once in the primary outcome). This also occurred with the overall sum for the incidences of hospitalizations as a component of the primary outcome.

Appendix 5: Additional References of Potential Interest

Systematic Reviews – Different Comparators

Gregorio GV, Gonzales ML, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database Syst Rev*. 2016 12 13;12:CD006519.

Freedman SB, Pasichnyk D, Black KJ, et al. Gastroenteritis therapies in developed countries: systematic review and meta-analysis. *PLoS ONE*. 2015;10(6):e0128754.

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