Original Investigation

Effect of Dilute Apple Juice and Preferred Fluids vs Electrolyte Maintenance Solution on Treatment Failure Among Children With Mild Gastroenteritis
A Randomized Clinical Trial

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IMPORTANCE Gastroenteritis is a common pediatric illness. Electrolyte maintenance solution is recommended to treat and prevent dehydration. Its advantage in minimally dehydrated children is unproven.

OBJECTIVE To determine if oral hydration with dilute apple juice/preferred fluids is noninferior to electrolyte maintenance solution in children with mild gastroenteritis.

DESIGN, SETTING, AND PARTICIPANTS Randomized, single-blind noninferiority trial conducted between the months of October and April during the years 2010 to 2015 in a tertiary care pediatric emergency department in Toronto, Ontario, Canada. Study participants were children aged 6 to 60 months with gastroenteritis and minimal dehydration.

INTERVENTIONS Participants were randomly assigned to receive color-matched half-strength apple juice/preferred fluids (n=323) or apple-flavored electrolyte maintenance solution (n=324). Oral rehydration therapy followed institutional protocols. After discharge, the half-strength apple juice/preferred fluids group was administered fluids as desired; the electrolyte maintenance solution group replaced losses with electrolyte maintenance solution.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of treatment failure defined by any of the following occurring within 7 days of enrollment: intravenous rehydration, hospitalization, subsequent unscheduled physician encounter, protracted symptoms, crossover, and 3% or more weight loss or significant dehydration at in-person follow-up. Secondary outcomes included intravenous rehydration, hospitalization, and frequency of diarrhea and vomiting. The noninferiority margin was defined as a difference between groups of 7.5% for the primary outcome and was assessed with a 1-sided α=.025. If noninferiority was established, a 1-sided test for superiority was conducted.

RESULTS Among 647 randomized children (mean age, 28.3 months; 331 boys [51.1%]; 441 (68.2%) without evidence of dehydration), 644 (99.5%) completed follow-up. Children who were administered dilute apple juice experienced treatment failure less often than those given electrolyte maintenance solution (16.7% vs 25.0%; difference, −8.3%; 97.5% CI, −∞ to −2.0%; $P < .001$ for inferiority and $P = .006$ for superiority). Fewer children administered apple juice/preferred fluids received intravenous rehydration (2.5% vs 9.0%; difference, −6.5%; 99% CI, −11.6% to −1.8%). Hospitalization rates and diarrhea and vomiting frequency were not significantly different between groups.

CONCLUSIONS AND RELEVANCE 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 as desired may be an appropriate alternative to electrolyte maintenance fluids in children with mild gastroenteritis and minimal dehydration.

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The annual burden of acute gastroenteritis in the United States includes 178.8 million related episodes and 473 832 hospitalizations.[1] Pediatric gastroenteritis therapy is focused on oral rehydration solution administration to prevent and treat dehydration[2] whenever diarrhea occurs.[3,4]Evidence supporting this approach has emerged primarily from low- and middle-income countries. Similar benefits may not arise from routine electrolyte maintenance solution administration in locations where significant dehydration is uncommon.

Electrolyte maintenance solution is relatively expensive[5,6] and its taste can limit use.[6] In a survey, 62% of caregivers stated a preference for intravenous rehydration rather than ongoing electrolyte maintenance solution administration for their child with gastroenteritis.[7] Challenges associated with electrolyte maintenance solution administration often result in intravenous rehydration when children are brought for emergency department (ED) care.[8,9] Thus, there remains a need to improve oral rehydration success in children with minimal dehydration.

To address this question, we randomized children seeking ED care with gastroenteritis and minimal dehydration to consume half-strength apple juice followed by their preferred fluids or to the exclusive use of electrolyte maintenance solution to replace losses.[4] We hypothesized that allowing children to drink dilute apple juice followed by their preferred fluids would not result in an increased frequency of treatment failure compared with electrolyte maintenance solution use.

Methods

Design and Setting

We performed a single-center, randomized, single-blind noninferiority trial (**Figure 1**) in the ED of a tertiary care pediatric hospital in Toronto, Ontario, Canada, that provides care to approximately 55 000 children annually, including approximately 3000 children with gastroenteritis.

Study Population

Following triage, research nurses evaluated potentially eligible children 6 days per week, 12 hours per day, between October and April of the 2010 to 2015 calendar years. Eligible children were aged 6 months to 60 months who presented with the following: 3 or more episodes of vomiting or diarrhea[10] in the preceding 24 hours; less than 96 hours of symptoms; weight of 8 kg (17.7 lb) or higher; and minimal dehydration.[4] Dehydration was quantified using the 4-item, 8-point Clinical Dehydration Scale.[8,11-14] Children with Clinical Dehydration Scale scores lower than 5 and capillary refill of less than 2 seconds[15] were classified as having minimal dehydration. Children were excluded if they had a history of chronic gastrointestinal disease (eg, inflammatory bowel disease, celiac disease) or other diseases (eg, diabetes mellitus, inborn errors of metabolism) that complicated the clinical picture; prematurity with corrected postnatal age of less than 30 weeks; bilious vomiting, hematemesis, hematochezia, or clinical concern for acute abdomen; or a need for immediate intravenous rehydration (eTable 1 in Supplement 1). Only Ontario residents were eligible to enable data verification from provincial registries. The protocol and analysis plan (Supplement 2) was approved by the hospital's research ethics board. Guardians of all participants provided written informed consent.

Allocation

Children were randomly assigned to receive half-strength apple juice/preferred fluids or electrolyte maintenance solution in a 1:1 ratio using computer-generated blocks of 8. The study team was unaware of the block sizes. Research support pharmacy staff, who were not responsible for patient selection, enrollment, or treatment allocation, created and stored the randomization table, which they used to prepare the study solutions and randomization assignment instructions. The latter were inserted into identical, opaque, sealed envelopes that were consecutively numbered on the outside and stored in a locked cabinet. Color-matched, refrigerated study solutions were prepared in opaque, identical-appearing bottles (eAppendix 1 in Supplement 1). The randomized discharge instructions were directly provided to families on ED discharge. Guardians opened the envelope at home. Nurses responsible for data collection did not participate in randomization envelope preparation. Randomization table assignments were not disclosed until analyses were finalized.

Study Interventions

The study protocol (eFigure in Supplement 1) was initiated immediately following triage and prior to physician evaluation to minimize contamination through electrolyte maintenance solution provision. The intervention group received half-strength apple juice; the control group received apple-flavored, sucralose-sweetened Pediatric Electrolyte (Pharmascience), an electrolyte maintenance solution. All participants received 2 L of their assigned solution for use in the ED and at home following discharge. Nonexperimental ED treatments were implemented according to accepted standards[3,4,16] and institutional guidelines.

Children received 5-mL aliquots of the assigned fluid every 2 to 5 minutes. Those who vomited received oral ondansetron.[17,18] All children underwent ED physician evaluation; treatment decisions were at the discretion of the responsible physician. If oral consumption or hydration status were unsatisfactory, the physician could continue oral rehydration with the same or alternate (ie, crossover) solution or administer intravenous hydration.

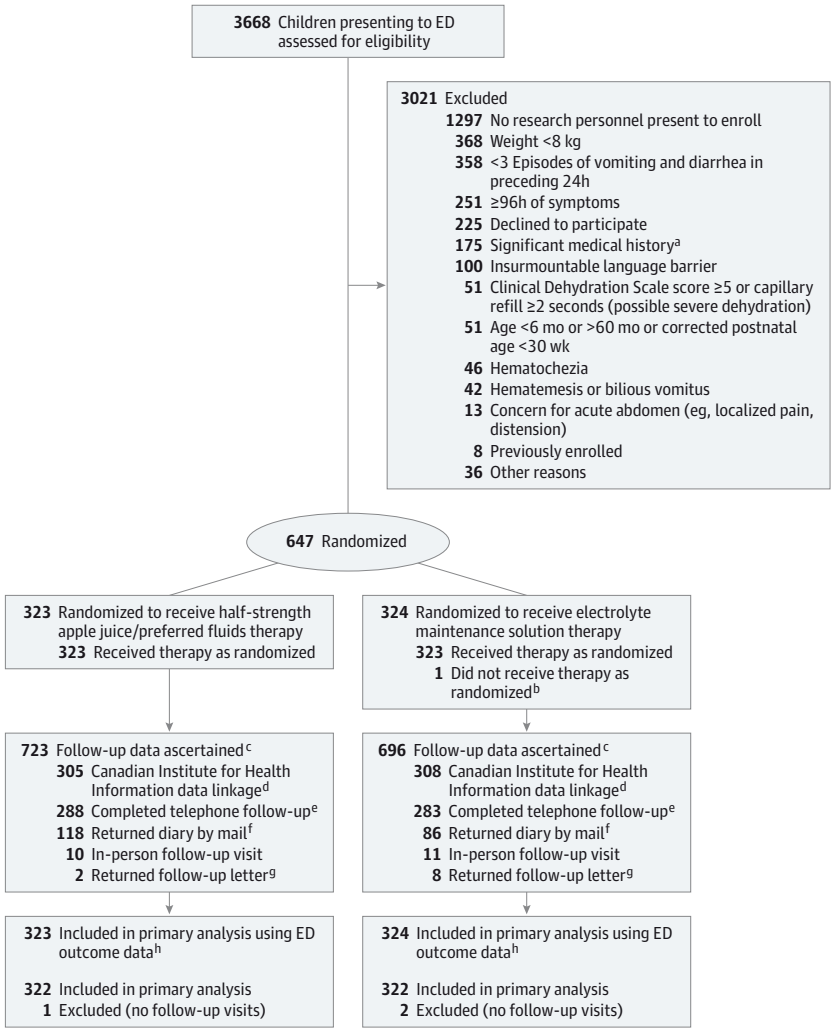
Postdischarge Care

On the opaque envelope containing the home allocation assignment, the research nurse specified the fluid volume to be provided to replace losses: 2 mL/kg per vomiting episode and 10 mL/kg per diarrheal episode.[4] Children in both groups received discharge instructions with the contents regarding recommended rehydration solutions removed. Families were given the option of research nurse reevaluation 72 to 84 hours after enrollment.

Dilute Apple Juice/Preferred Fluids Group

Caregivers were instructed to provide liquids other than electrolyte maintenance solution in keeping with their child's usual

Figure 1. Screening, Randomization, and Follow-up



[a] Significant medical history includes all children with known gastrointestinal diseases (ie, inflammatory bowel disease, celiac disease) or any other underlying disease process that might place the child at an increased risk of treatment failure.

[b] One child did not receive electrolyte maintenance solution as randomized during the period between randomization and provision of study medications; the family left the emergency department (ED). The family was contacted to enable provision of the supplies but declined to initiate their use at that time.

[c] These categories are not mutually exclusive.

[d] Reasons for absent Canadian Institute for Health Information data: 6 cases with enrollment dates after April 1, 2015 (data unavailable until 2016), 13 with invalid health care numbers, and 12 without any data.

[e] Caregivers were contacted daily to track outcomes (revisits, intravenous fluid administration, and hospitalization). Calls were be made by a research nurse using a standardized set of questions and responses to caregiver queries.

[f] All participants were provided a diary in which to record follow-up health care clinician visits, diarrhea, vomiting, child care, expenses, and fluids administered. These were returned at the final in-person reassessment or by mail.

[g] To promote the collection of outcome data, a letter was sent by registered mail to all families not contacted by telephone after 7 days requesting that they either contact the research nurse by telephone or complete and return a data form focused on the outcome measures.

[h] Primary analysis using ED outcome data refers to the analysis conducted including all study participants who had ED outcome data available. Primary analysis refers to the analysis performed including only participants who had follow-up data collected.

dietary pattern (eg, juices or milk; eAppendix 2 in Supplement 1) to replace losses. Children were permitted to consume beverages with high content of simple sugars such as the study intervention solution (ie, half-strength apple juice) or sports beverages, which are contraindicated in most guidelines.[3,4]

Electrolyte Maintenance Solution Group

The instructions specified that the electrolyte maintenance solution provided was to be used to replace all losses (eAppendix 3 in Supplement 1). Fluids containing nonphysiological concentrations of glucose and electrolytes were discouraged.[3,4]

Follow-up

Caregivers were telephoned daily by a research nurse who was blinded to treatment assignment until the child had been asymptomatic for 24 hours. Standardized criteria were used to guide recommendations (eg, eAppendix 4 in Supplement 1). A registered letter was sent to families not contacted after 5 telephone

attempts. Caregivers were provided a diary in which to record key details such as follow-up health care clinician visits and diarrhea and vomiting frequency. These were returned at the final in-person reassessment or by mail. Data verification for ED revisits, hospitalization, and adverse events was obtained from 2 provincial registries, the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which includes hospital discharge diagnoses from all hospitals in the province, and the National Ambulatory Care Reporting System (NACRS), which includes ED visit diagnoses.

Study Outcomes

The primary outcome of treatment failure was a composite measure defined by any of the following occurring within 7 days of enrollment: (1) hospitalization or intravenous rehydration; (2) subsequent unscheduled physician encounter in an office, urgent care, or ED setting for the same episode of vomiting or diarrhea[19] (ie, "episode" terminates when symptom free for 24 hours); (3) protracted symptoms (ie, ≥3 episodes of vomiting or diarrhea within a 24-hour period occurring >7 days after enrollment); (4) physician request to administer a solution representing treatment allocation crossover at the index visit; or (5) a 3% or greater weight loss or Clinical Dehydration Scale score of 5 or higher at in-person follow-up.

Secondary outcomes identified a priori were (1) intravenous rehydration at the index visit or a subsequent visit within 7 days of enrollment; (2) hospitalization at the index visit or a subsequent visit; (3) frequency of diarrhea and vomiting; and (4) percentage weight change at the 72- to 84-hour reassessment.[20-22] Planned exploratory outcomes included serum sodium, potassium, bicarbonate, urea, and creatinine among children receiving intravenous rehydration at a revisit; time to return to a 75% "normal" diet; and caregiver satisfaction with the discharge instructions provided and the ease of implementation, evaluated at first in-person follow-up visit. Post hoc analyses of the individual components of the primary composite outcome were also conducted. All diagnoses associated with health care visits as coded in the CIHI and NACRS databases occurring within 14 days of the index ED visit were reviewed to identify adverse events (eg, hyponatremia, seizure, intensive care unit admission).

Statistical Analysis

Sample size was based on the composite primary outcome of treatment failure and the null hypothesis that the probability of treatment failure in the apple juice/preferred fluids group was at least 7.5% higher than that in the electrolyte maintenance solution group; the alternative hypothesis was no difference. Enrolling 624 participants yielded 80% power to reject the null hypothesis (ie, apple juice/preferred fluids is inferior) when the alternative was true, using a 1-sided α=.025. Sample size was determined using an estimated 15% failure probability in the electrolyte maintenance solution group[23] and a 10% loss to follow-up[18] (PASS 2008, version 08.0.2; NCSS). Rejecting the null hypothesis would lead to the conclusion that apple juice followed by preferred fluids was not inferior and could be considered a therapeutic option. The noninferiority margin of 7.5% was set only for the primary end point, was determined through a focus group discussion with experts in the field, and was based on the difference participants were willing to accept in exchange for the perceived benefits associated with apple juice use along with other fluids as desired.

Analyses were undertaken by intention-to treat principles. Continuous data are presented as means with standard deviations and medians with interquartile ranges (IQRs). The primary efficacy analysis evaluated noninferiority by calculating the 95% confidence interval for the difference in probability of failure (ie, apple juice/preferred fluids minus electrolyte maintenance solution). If the upper bound of the 95% CI for this difference was less than the inferiority margin (ie, +7.5%), inferiority could be rejected. If noninferiority was confirmed, a test for superiority would be conducted at the 1-sided α=.025 level, according to the recommendation of the Committee for Proprietary Medicinal Products.[24] Comparisons between groups for the secondary outcomes were performed using an independent sample *t* test for continuous variables, the Fisher exact test for categorical variables, and the Wilcoxon rank-sum test for non-normally distributed variables. A Bonferroni correction was used to assess statistical significance for the secondary outcomes, and significance was set at the *P*=.01 (ie, .05/5) level. Frequency of diarrhea and vomiting follow a Poisson distribution[18] and were analyzed with a regression model following that assumption.

A planned exploratory analysis evaluated the interaction between age and treatment effect. A logistic regression model was used containing the following independent variables: an indicator variable for treatment group; age in years; the natural log of age; and the interactions between both treatment group and age and group and the natural log of age. The model depicting treatment failure as a function of age was displayed graphically to facilitate interpretation and includes the threshold odds ratio for noninferiority.

An independent data and safety monitoring committee performed an interim analysis after 200 participants were recruited. They adopted the option of stopping the study if a benefit in favor of electrolyte maintenance solution was shown such that the nominal significance levels proposed by Haybittle[25] were met: a probability value of .001 for the interim analysis and .025 for the final analysis. Analyses were performed with SPSS, version 19.0.0.1 (SPSS Inc) and SAS, version 9.4 (SAS Institute Inc).

Results

Patients

Among 647 randomized children (mean age, 28.3 [SD, 15.9] months; 331 boys [51.1%]; 441 [68.2%] without clinical evidence of dehydration) (Figure 1), 323 were randomized to apple juice/preferred fluids therapy and 324 to electrolyte maintenance solution. Baseline characteristics were not different between the groups (**Table 1**). The 225 children whose caregivers declined participation were less likely to receive ondansetron, but otherwise the groups were not significantly different (eTables 2 and 3 in Supplement 1).

A total of 99.5% of participants (644/647) had data ascertained from at least 1 follow-up method. Follow-up data

Table 1. Baseline Characteristics of the Randomized Treatment Groups

Characteristics	All Patients (n = 647)	Half-Strength Apple Juice/Preferred Fluids Therapy (n = 323)	Electrolyte Maintenance Solution Therapy (n = 324)
Age, mean (SD), mo	28.3 (15.9)	28.0 (15.4)	29.0 (16.5)
Male sex, No. (%)	331 (51.1)	173 (53.6)	158 (48.8)
Weight, mean (SD), kg	14.8 (11.4)	14.9 (12.1)	14.6 (10.2)
Enrollment time, mean (SD), 24-h clock	15:26 (3:27)	15:20 (3:35)	15:32 (3:18)
History of vomiting, No. (%)	610 (94.3)	306 (94.7)	304 (93.8)
Time interval between vomit onset and ED visit, mean (SD), h[a]	30.7 (22.8)	30.9 (22.9)	30.5 (22.7)
Vomiting episodes in preceding 24 h, median (IQR)[a]	5 (3-7)	5 (3-7)	5 (3-6)
History of diarrhea, No. (%)	274 (42.4)	136 (42.1)	138 (42.6)
Time interval between diarrhea onset and ED visit, mean (SD), h	36.6 (25.9)	36.1 (25.2)	37.1 (26.7)
Diarrhea episodes in preceding 24 h, median (IQR)[a]	3 (2-6)	3 (2-6)	3 (2-6)
Rotavirus vaccine received, No. (%)[b]	182 (28.1)	93 (28.8)	89 (27.5)
Baseline Clinical Dehydration Scale score, median (IQR)[c]	0 (0-1)	0 (0-1)	0 (0-1)
Baseline Clinical Dehydration Scale score distribution, No. (%)[c]			
0	441 (68.2)	219 (67.8)	222 (68.5)
1	88 (13.6)	42 (13.0)	46 (14.2)
2	77 (11.9)	39 (12.1)	38 (11.7)
3	21 (3.3)	8 (2.5)	13 (4.0)
4	20 (3.1)	15 (4.6)	5 (1.5)
Baseline general appearance, Clinical Dehydration Scale score, mean (SD)			
Normal (0 points)	512 (79.1)	252 (78.0)	260 (80.2)
Thirsty, restless, lethargic but irritable when touched (1 point)	130 (20.1)	68 (21.1)	62 (19.1)
Drowsy, limp, cold, sweaty, comatose (2 points)	5 (0.8)	3 (0.9)	2 (0.6)
Ondansetron administered, No. (%)	436 (67.4)	214 (66.3)	222 (68.5)

Abbreviations: ED, emergency department; IQR, interquartile range.

[a] Only children with presence of any vomiting or diarrhea were included.

[b] Rotavirus vaccine status was self-reported.

[c] The Clinical Dehydration Scale score is a 4-item score used to estimate dehydration severity in children with gastroenteritis. The score ranges from 0 to 8; a value of 0 to 2 points is assigned to general appearance, sunken eyes, oral mucosa, and tears. Higher scores reflect more significant dehydration.[12-14,40]

collection occurred through CIHI data linkage (94.7%; 613/647), telephone (88.3%; 571/647), diary (31.5%; 204/647), in-person visit (3.3%; 21/647), and letter (1.6%; 10/647).

Primary Outcome

In the intention-to-treat analysis, which encompassed all events occurring at the index visit and during follow-up, the treatment failure rate was 16.7% (54/323; 95% CI, 12.8%-21.2%) in the apple juice/preferred fluids and 25.0% (81/324; 95% CI, 20.4%-30.1%) in the electrolyte maintenance solution group (difference, −8.3%; 97.5% CI, −∞ to −2.0) (**Table 2**). These findings are consistent with noninferiority, with the upper bound of the 1-sided 97.5% CI for the difference in failure being less than the prespecified noninferiority margin of +7.5%. The *P* value for the null hypothesis of inferiority was *P*<.001. Testing for superiority yielded a *P*=.006. Including only participants with available follow-up after the index ED visit yielded a failure rate of 16.8% (54/322; 95% CI, 13.1%-22.0%) in the apple juice/preferred fluids group and 25.2% (81/322; 95% CI, 20.0%-30.2%) in the electrolyte maintenance solution group (difference, −8.4%; 97.5% CI, −∞ to −2.1%; *P*<.001 for inferiority).

Exploratory analysis identified a nonlinear interaction between treatment assignment and age (**Figure 2** and Table 2). The threshold odds ratio of 1.44 was calculated using the treatment failure rate in the control group (25%) and the threshold failure rate for the intervention group (32.5%). The latter was calculated by adding the a priori-determined margin of noninferiority (7.5%) to the study treatment failure rate in the control group. The combined test of significance for the interaction and the nonlinearity of the interaction was *P* = .01. In the model, the benefit of apple juice/preferred fluids over electrolyte maintenance solution was most notable in children aged 24 months or older (<24 months: apple juice/preferred fluids [38/159; 23.9%] vs electrolyte maintenance solution [38/158; 24.1%], difference, −0.1% [95% CI, −9.5% to 9.2%]; ≥24 months: apple juice/preferred fluids [16/164; 9.8%] vs electrolyte maintenance solution [43/166; 25.9%], difference, −16.2% [95% CI, −24.2% to −8.0%]) (Table 2 and Figure 2).

Post hoc examination of the individual elements of the composite primary outcome revealed a lower overall 7-day intravenous rehydration rate among children administered apple juice/preferred fluids compared with electrolyte maintenance solution (apple juice/preferred fluids, 2.5% [8/323] vs

Table 2. Composite Primary and Secondary Outcomes in the Study Groups[a]

Outcomes	Half-Strength Apple Juice/ Preferred Fluids Therapy		Electrolyte Maintenance Solution Therapy		Difference, % (95% CI)	*P* Value
	No./Total	% (95% CI)	No./Total	% (95% CI)		
Composite primary outcome: overall treatment failure, any criteria[b]	54/323	16.7 (12.8-21.2)	81/324	25.0 (20.4-30.1)	−8.3 (−∞ to −2.0)[c]	<.001[d]
Age, mo						
6 to <12	7/45	15.6 (7.8-28.8)	15/48	31.3 (20.0-45.3)	−13.6 (−29.7 to 3.6)	
12 to <18	20/69	29.0 (19.6-40.6)	14/70	20.0 (12.3-30.8)	9.0 (−5.3 to 22.9)	
18 to <24	11/45	24.4 (14.2-38.7)	9/40	22.5 (12.3-37.5)	1.9 (−16.2 to 19.4)	
24 to <30	5/37	13.5 (5.9-28.0)	10/44	22.7 (12.8-37.0)	−9.2 (−25.4 to 8.3)	
30 to <36	2/23	8.7 (2.4-26.8)	5/19	26.3 (11.8-48.8)	−17.6 (−41.0 to 5.6)	
36 to <42	2/28	7.1 (2.0-22.6)	3/15	20.0 (7.1-45.2)	−12.9 (−38.6 to 7.3)	
42 to <48	3/28	10.7 (3.7-27.2)	5/21	23.8 (10.6-45.1)	−13.1 (−35.5 to 8.0)	
48 to <54	3/27	11.1 (3.9-28.1)	6/27	22.2 (10.6-40.8)	−11.1 (−31.0 to 9.4)	
54 to <60	1/21	4.8 (0.9-22.7)	14/40	35.0 (22.1-50.5)	−30.2 (−46.2 to −8.2)	
Components of primary outcome						
Unscheduled health care visit	41/323	12.7 (9.3-16.8)	52/324	16.1 (12.2-20.5)	−3.4 (−10.5 to 3.8)[e]	.26
Emergency department	20/323	6.2 (3.8-9.4)	30/324	9.3 (6.3-13.0)	−3.1 (−8.7 to 2.5)[e]	
Family physician	12/323	3.7 (1.9-6.4)	13/324	4.0 (2.2-6.8)	−0.3 (−4.6 to 4.0)[e]	
Pediatrician	4/323	1.2 (0.3-3.1)	6/324	1.9 (0.7-4.0)	−0.6 (−3.8 to 2.5)[e]	
Walk-in clinic	6/323	1.9 (0.7-4.0)	4/324	1.2 (0.3-3.1)	0.6 (−2.4 to 3.9)[e]	
Unspecified[f]	2/323	0.6 (0.08-2.2)	1/324	0.3 (0.01-1.7)	0.3 (−2.0 to 2.8)[e]	
Weight loss/dehydration at follow-up 72-84 h after index visit[g]	2/10	20.0 (2.5-55.6)	1/10	10.0 (0.3-44.5)	10.0 (−33.8 to 50.9)[e]	.99
IV rehydration[h]	8/323	2.5 (1.1-4.8)	29/324	9.0 (6.1-12.6)	−6.5 (−11.6 to −1.8)[e]	.001
Hospitalization	3/323	0.9 (0.2-2.7)	9/324	2.8 (1.3-5.2)	−1.9 (−5.4 to 1.3)[e]	.14
Extended symptomatology[i]	9/297	3.0 (1.4-5.7)	4/294	1.4 (0.4-3.5)	1.7 (−1.9 to 5.6)[e]	.26
Crossover[j]	2/323	0.6 (0.08-2.2)	9/324	2.8 (1.3-5.2)	−2.2 (−5.7 to 0.8)[e]	.06
Secondary outcomes						
IV rehydration at index ED visit	3/323	0.9 (0.2-2.7)	22/324	6.8 (4.3-10.1)	−5.9 (−10.5 to −2.0)[e]	<.001
IV rehydration during follow-up within 7 d of index visit	6/323	1.9 (0.7-4.0)	11/324	3.4 (1.7-6.0)	−1.5 (−5.4 to 2.1)[e]	.33
Hospitalization at index visit	1/323	0.3 (0.01-1.7)	6/324	1.9 (0.7-4.0)	−1.5 (−4.7 to 1.0)[e]	.12
Hospitalization at follow-up within 7 d of index visit	3/323	0.9 (0.2-2.7)	5/324	1.5 (0.5-3.6)	−0.6 (−3.7 to 2.3)[e]	.73
					Rate Ratio (99% CI)	*P* Value
Diarrhea episodes, electrolyte maintenance solution:half-strength apple juice[k]					1.14 (0.79 to 1.64)	.60
Vomiting episodes, electrolyte maintenance solution:half-strength apple juice[k]					1.07 (0.77 to 1.49)	.39

Abbreviations: ED, emergency department; IV, intravenous.

[a] *P* values for comparisons used 2-sided Fisher exact test unless noted. Totals within outcomes may be lower than individual items because some children experienced the same outcome more than once. Significance of components of primary outcome and all secondary outcomes was set at *P*<.01. *P* values are reported for a priori–specified primary and secondary outcomes and post hoc analyses of components of the primary outcome.

[b] Treatment failure defined as any of (1) IV rehydration at index ED visit; (2) subsequent unscheduled office, urgent care, or ED visit for the same episode of vomiting/diarrhea (episode ends when symptom free for 24 hours); (3) protracted symptoms (ie, ≥3 episodes of vomiting/diarrhea within 24-hour period >7 days after enrollment); (4) physician request to administer a solution representing treatment allocation crossover; or (5) ≥3% weight loss or Clinical Dehydration Scale score ≥5 at in-person follow-up. This outcome includes all enrolled children; even those without complete follow-up (n = 3) could have treatment failure through IV rehydration at the index ED visit.

[c] Confidence interval for the primary outcome represents a 1-sided 97.5% CI.

[d] *P* value for the primary outcome reflects testing the null hypothesis (the proportion of treatment failures in the half-strength apple juice/preferred fluids therapy group is at least 7.5 percentage points higher than that in the electrolyte maintenance solution group).

[e] Confidence intervals are 99% CIs.

[f] Patients with unspecified data had unscheduled health care visits reported only on the follow-up letter that caregivers completed at home.

[g] A ≥3% weight loss or Clinical Dehydration Scale score ≥5 at in-person follow-up; only 20 children were seen in scheduled follow-up.

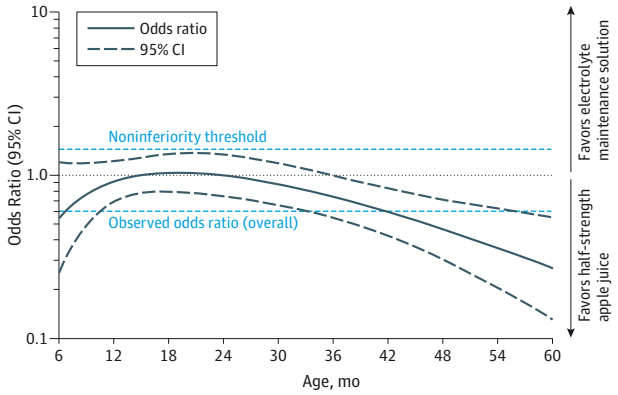
[h] Overall number is less than sum of index and follow-up because some children experienced the outcome at both index and follow-up.

[i] Extended symptomology includes children with protracted symptoms (ie, ≥3 episodes of vomiting or diarrhea within a 24-hour period occurring >7 days after enrollment) among those for whom diary or telephone follow-up was completed.

[j] Crossover was defined by consumption by a participant during index ED visit of the solution provided to participants from the other study group (eTable 4 in Supplement 1).

[k] Frequency of diarrhea and vomiting follow a Poisson distribution and were analyzed with a regression model following that assumption.

Figure 2. Treatment Failure Comparing Half-Strength Apple Juice/Preferred Fluids Therapy and Electrolyte Maintenance Solution Groups as a Function of Age



The threshold odds ratio of 1.44 for noninferiority is based on the actual failure rate (25%) in the electrolyte maintenance solution group in our study using the a priori–determined margin of noninferiority (7.5%), yielding the threshold failure rate of 32.5% for the half-strength apple juice/preferred fluids group. The observed odds ratio was 0.60 (ignoring age). A nonlinear relationship was identified among age, treatment failure, and treatment group (ie, half-strength apple juice/preferred fluids or electrolyte maintenance solution). The best model contained a term for group, age, the natural log of age, and the interactions between group and age and group and the natural log of age. The model on which this figure is based is specified in eAppendix 5 in Supplement 1 and was generated from the estimated parameters (log odds ratios and corresponding variances and covariances) from the logistic regression model.

electrolyte maintenance solution, 9.0% [29/324]; difference, −6.5%; 99% CI, −11.6% to −1.8%). Hospitalization rates were 0.9% (3/323) vs 2.8% (9/324) in the apple juice/preferred fluids and electrolyte maintenance solution groups, respectively (difference, −1.9%; 99% CI, −5.4% to 1.3%). Subsequent unscheduled medical visits, extended symptomatology, crossover at the index ED visit, and weight loss or dehydration at follow-up did not differ significantly between groups (Table 2 and eTable 4 in Supplement 1).

Secondary Outcomes

Intravenous rehydration administration at the index ED visit was less frequent in the apple juice/preferred fluids group (apple juice, 0.9% [3/323] vs electrolyte maintenance solution, 6.8% [22/324]; difference, −5.9%; 99% CI, −10.5% to −2.0%) (Table 2). Reasons for intravenous rehydration at the index visit included ongoing dehydration (n = 10), inadequate oral intake (n = 6), vomiting (n = 3), and other (n = 6). Diarrhea and vomiting episodes were not significantly different between groups (rate ratio, electrolyte maintenance solution:apple juice/preferred fluids, 1.14 [99% CI, 0.79-1.64; P = .39] for diarrhea and 1.07 [99% CI, 0.77-1.49; P = .60] for vomiting) (Table 2 and eTable 5 in Supplement 1). Median percentage weight change at reassessment was 0.00% (IQR, −0.55% to 0.37%) in the apple juice/preferred fluids group and −1.19% (IQR, −3.58% to 0.43%) in the electrolyte maintenance solution group (P = .18).

Two children were hyponatremic (1 in the apple juice/preferred fluids group with sodium level of 133 mEq/L and 1 in the electrolyte maintenance solution group with sodium level of 134 mEq/L) at the time of intravenous insertion. No other adverse events were reported or identified. In 598 of 617 cases (96.9%), the physicians reported being unaware of the randomization assignment; they judged assignment correctly in 2 of 4 children (50%) in the apple juice/preferred fluids group and 11 of 15 (73%) in the electrolyte maintenance solution group (P = .16). Insufficient data were available to evaluate electrolytes at revisit, caregiver satisfaction, or ease of protocol adherence.

Discussion

In this single-center trial in a high-income country, children with mild gastroenteritis and minimal dehydration experienced fewer treatment failures when offered dilute apple juice followed by their preferred fluid choice compared with those instructed to drink electrolyte maintenance solution to replace fluid losses. The benefit was greatest among children older than 24 months. Dilute apple juice administration followed by desired fluids resulted in a reduction in the intravenous rehydration rate.

These results challenge the recommendation to routinely administer electrolyte maintenance solution when diarrhea begins.[4] This recommendation is based primarily on an unblinded study in which blocks of participants were provided instructions for use of electrolyte maintenance solution or instructions plus a prescription for electrolyte maintenance solution at no charge.[19] Although a reduction in unscheduled follow-up care was noted, the number needed to treat was 16 (95% CI, 8-508) and no differences were noted in ED visits or hospitalization.[19] Although performed post hoc, our findings differed because we did not find differences in unscheduled visits between groups. The present study findings, derived from a larger and more heterogeneous population, confirmed via provincial registries, and conducted in an era when complicated episodes of gastroenteritis have become uncommon,[26] may more accurately reflect the effect rehydration fluid choice has on unscheduled medical visits.

The use of beverages with high sugar content has traditionally been discouraged because of their potential to induce an osmotic diarrhea.[3,4,27] However, studies evaluating this issue have found the effect to be minimal. Brazilian investigators randomized 90 children with severe diarrhea to consume water, apple juice, or grape juice.[28] Although those receiving juice had more stool losses on the first day, no differences persisted beyond the first day. Children fed juice ingested more calories and had greater weight gain. In a trial of 75 adults admitted with gastroenteritis in India, stool frequency, consistency, and body weight improved similarly among those randomized to an electrolyte maintenance solution (139 mmol/L of glucose) or a high-sugar-content sports drink (111 mmol/L of glucose and 117 mmol/L of sucrose).[29] In the current study, the frequency of diarrheal stools was not significantly different between study groups despite the permitted use of high-glucose fluids in the apple juice/preferred fluids group. These results provide pragmatic evidence that in

children with minimal dehydration, promoting fluid consumption is more important than the glucose load consumed.

A concern related to the administration of hyponatremic solutions is the risk of water intoxication.[30,31] Although the current study monitored for the occurrence of hyponatremia through daily follow-up and a provincial registry, no episodes of significant hyponatremia were identified. Such events have become rare and are more likely to occur in infants[32] experiencing significant diarrheal salt losses. The decline in severe rotavirus disease in developed countries has further reduced the frequency of this outcome. Moreover, the intentional exclusion of high-risk children (ie, aged <6 months) is an important consideration when nonelectrolyte maintenance solutions are administered.

The use of intravenous rehydration in the study's target population was minimized through a focus on the key contributing risk factors—vomiting and failure to drink.[18,33] To minimize vomiting, ondansetron was administered in accordance with our institutional protocol at a frequency in keeping with current usage trends in pediatric gastroenteritis.[34] To maximize electrolyte maintenance solution palatability, a refrigerated,[35] sucralose-sweetened solution was provided.[36] Despite these measures, the key difference between groups was the greater frequency of intravenous rehydration in the electrolyte maintenance solution group. The plausibility of the results presented is supported by exploratory analysis, which identified an interaction between age and the intervention: older children, who are more accustomed to drinking apple juice and other sweet beverages,[37] are less likely to become dehydrated, and are more taste discriminating[35] than younger children, experienced the greatest benefit from the dilute apple juice/preferred fluids diet.

A previous study evaluating sucralose-sweetened apple-flavored electrolyte solutions reported a palatability score of only 64 mm (SD, 8 mm) on a 100-mm visual analog scale, and only 70% of participants (children without evidence of enteric infection) indicated that they would drink the solution again.[36] Moreover, refusal to drink has been identified as the most common reason pediatric emergency medicine physicians provide intravenous rehydration to children in lieu of oral rehydration.[38] Given that the results presented demonstrate neither concerns regarding unblinding (which most likely would have led to the increased use of intravenous rehydration in the dilute apple juice/preferred fluids group) nor differential use of other adjunctive therapies (eg, ondansetron), these findings most likely reflect the effect of the intervention.

Several limitations should be considered. This study was conducted in a high-income country. Because children in low- and middle-income countries are at higher risk of gastroenteritis-related complications, the results should not be extrapolated to such settings. This was a single-center study and the control solution was an apple-flavored, sucralose-sweetened electrolyte maintenance solution; generalizability of study results to other settings and electrolyte maintenance solutions is uncertain. Although 68% of study participants had no evidence of dehydration (ie, Clinical Dehydration Scale score of 0), this is similar to dehydration characteristics reported in other ED-based studies.[8,12] Nonetheless, according to a statement endorsed by the American Academy of Pediatrics, oral rehydration solution should be used, even in children without evidence of dehydration, to compensate for losses.[39]

Children were not blinded to taste, and this may have resulted in unblinding of clinical team members in the ED. However, physician blinding assessment did not confirm this theory. Taste matching was not performed because palatability differences were required to evaluate the effect of the interventions. The 2 study liquids were color matched to minimize unblinding of parents and physicians in the ED. Parents were not blinded to the home therapy assignment in order to guide their home fluid management strategy. In addition, volume of fluids consumed, patient adherence, and crossover at home were not measured; the latter 2 may have driven the difference in the primary outcome (ie, treatment failure) toward the null.

Conclusions

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.

ARTICLE INFORMATION

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