

Research

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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Apple juice for rehydration

Oral rehydration therapy (ORT) has been the preferred treatment for mild gastroenteritis (GE) globally for decades. Solutions containing glucose and electrolytes are undoubtedly effective, but there's a problem: they taste awful (ever tried one?). Young children who are feeling unwell are even less likely to drink something unpleasant than they would when well, so many carers abandon attempts to force it down: the result, sometimes, is the eventual need for intravenous fluids. Could this be prevented by giving something more palatable?

Researchers from Toronto, Canada set out to see whether dilute apple juice was as good as standard electrolyte maintenance solution (EMS), here sweetened with sucralose (Freedman S, *et al. JAMA*. 2016; doi:10.1001/jama.2016.5352). In a non-inferiority trial, they randomised over 640 children aged 6 months to 5 years presenting to a single large children's emergency department (ED). To qualify they needed to have mild GE, ie, no or only minimal dehydration clinically, and no other complicating conditions. The study was single-blind, so the caregivers knew what they were giving after discharge from the ED, and they were given specific instructions: the apple juice group could drink what they wanted, while the EMS group were asked to stick with a rehydration schedule. They were followed up by telephone contact after 48–72 hours. No lab tests were done. Treatment failure was defined as the need for admission or IV fluids, re-attendance, or symptoms persisting >7 days.

They found that the apple juice group did better (17% were treatment failures vs 25% in the EMS group: $p < 0.001$ for inferiority, $p = 0.006$ for superiority). IV fluids were given to 2.5% of the apple juice group and 9% of the EMS group. The difference was greatest for older children, perhaps because they are more fussy about what they drink. The higher sugar content of apple juice, which in theory could cause a pro-diarrhoeal osmotic effect, did not seem to be a problem.

It is important not to extrapolate these findings to low-income countries, and where the nature and severity of GE is very different. But here in the West, we can now feel more reassured about what many of us are saying to parents already: if the child won't drink electrolyte solution, ask them to drink dilute juice instead.

Competing interests None.

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Background:

- ✓ Soluzione reidratante orale (SRO) in gastroenterite (GE) quando si verifici diarrea
- ✓ Evidenza di paesi basso e medio *income*
- ✓ Non evidenza di beneficio in luoghi in cui disidratazione grave è non comune

Intervention:

- ✓ Bambini con GE e disidratazione minima
- ✓ Diluizione 50% succo di mela seguito da liquido preferito
- ✓ SRO

Hypothesis:

- ✓ Consentire idratazione con succo di mela seguito da liquido preferito non risulta in un incremento del fallimento del trattamento vs SRO



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Criteri inclusione:

- 3 o più episodi di diarrea o vomito nelle 24 h precedenti
- < 96 h di sintomi
- Peso \geq 8 kg
- Disidratazione minima

Criteri esclusione:

- Storia di malattia gastrointestinale cronica
- Altre malattie che possono complicare il quadro clinico
- Prematurità (< 30 sett eg)
- Vomito biliare
- Ematemesi
- Ematochezia
- Sospetto di addome acuto
- Necessità immediata reidratazione EV

Characteristic	Score of 0	Score of 1	Score of 2
General Appearance	Normal	Thirsty, restless or lethargic but irritable when touched	Drowsy, limp, cold or sweaty; comatose or not
Eyes	Normal	Slightly sunken	Very sunken
Mucous membranes (tongue)	Moist	Sticky	Dry
<u>Tears</u>	Tears	Decreased tears	Absent tears

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Intervention:

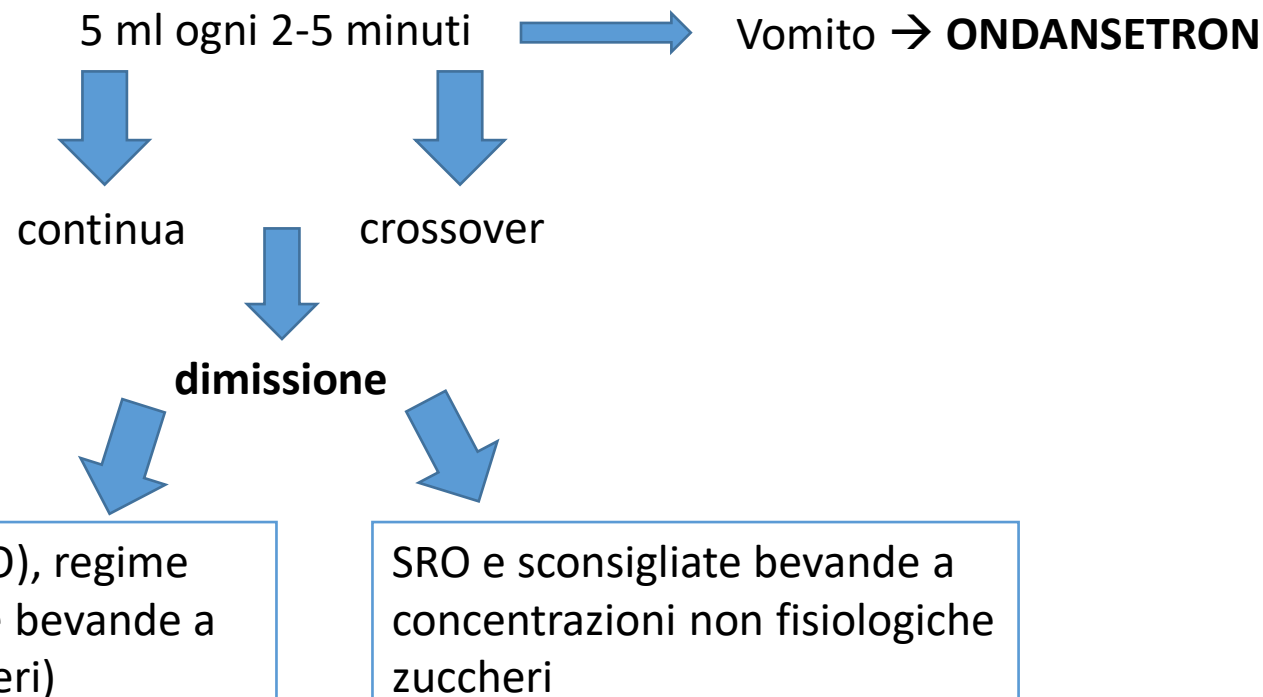
- ✓ Bambini con GE e disidratazione minima
- ✓ Diluizione 50% succo di mela seguito da liquido preferito
- ✓ SRO

Succo di mela diluito 50%

SRO elettrolitica con sapore di mela

Methods:

- ✓ 3000 bambini con GE
- ✓ 6 mesi – 60 mesi



Study Outcomes:

- 1. Fallimento terapeutico documentato da uno dei seguenti, entro 7 giorni dall'arruolamento:**
 - ✓ ospedalizzazione o idratazione EV
 - ✓ visita successiva non programmata dal medico, pronto soccorso per lo stesso episodio di vomito e diarrea
 - ✓ sintomi protratti (≥ 3 vomito o diarrea nelle 24 ore > 7 gg dopo arruolamento)
 - ✓ il medico richiede crossover
 - ✓ $\geq 3\%$ perdita peso o Clinical Dehydration score ≥ 5 al follow up
- 2. reidratazione EV alla prima visita o follow up entro 7 giorni da arruolamento**
- 3. ospedalizzazione alla prima visita o a una successiva**
- 4. frequenza di vomito e diarrea**
- 5. % variazione peso corporeo al follow up (72-84 ore)**



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Results 1:

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) ^b	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) ^b	3 (2-6)	3 (2-6)	3 (2-6)
Rotavirus vaccine received, No. (%) ^d	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)



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Results 2:

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 ^a	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) ^h	.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) ^h	.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) ^h	.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 ⁱ	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



Discussion:

Fallimento della reidratazione orale > causa ricorso a idratazione EV

GE lieve e minima disidratazione meno fallimenti terapeutici in reidratazione con succo di mela diluito + liquidi preferiti

Beneficio maggiore nei bambini > 24 mesi

Succo di mela diluito è seguito da una riduzione al ricorso di terapia EV

Bevande con **elevato contenuto di zuccheri** tradizionalmente scoraggiato per potenziale ruolo nell'indurre **diarrea osmotica**

Dimostrati effetti minimi – **promuovere il consumo di fluidi è più importante che il carico orale di glucosio consumato**

Problema con soluzioni iponatremiche → iponatremia

Intenzionale esclusione bambini ad elevato rischio (età < 6 mesi) – considerazione importante quando viene somministrata soluzione NON elettrolitica

Ondansetron



Conclusions:

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.



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