DRUG USED IN ACUTE DIARRHEA

PRO

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ESPGHAN Guideline

- Treatment
  - Rehydration therapy (Reduced osmolarity ORS) (I,A)
  - Nutritional management
  - Pharmacological therapy
    - Antisecretory: Racecadotril (II, B)
    - Probiotics: LGG (I,A), *S. boulardii* (II,B)
    - Adsorbents: Smectite (II, B)
    - Antiemetic

J Pediatr Gastroenterol Nutr 2008;46:S81-S122

ESPGHAN Guideline

Reduced or hypotonic osmolarity ORS should be used as first-line therapy for the management of children with AGE.

Noncholera diarrhea: Reduced osmolarity ORS is more effective than full strength ORS, as measured by clinically important outcomes such as reduced stool output, reduced vomiting, and reduced need for supplemental intravenous therapy (I, A).

The ESPGHAN solution has been used successfully in several RCTs and in a number of non-RCTs in European children. It may be used in children with AGE (II, A).

Cholera diarrhea: Although data were more limited, reduced osmolarity ORS also appears safe and effective for children with cholera (I, A).

J Pediatr Gastroenterol Nutr 2008;46:S81-S122

ORS

	WHO-reduced osmolarity	ESPGHAN-ORS	Classical WHO-ORS
Sodium (mmol/L)	75	60	90
Potassium (mmol/L)	20	20	20
Chloride (mmol/L)	65	25	80
Bicarbonate (mmol/L)	0	0	0
Citrate (mmol/L)	10	10	10
Glucose (mmol/L)	75	74-111	111
Osmolarity (mOsm/L)	245	200-250	311

Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

- Cochrane database analysis
- Standard WHO-ORS may not be optimal
- ORS that contain lower concentrations of sodium and glucose may be more effective
- 11 RCTs were analyzed

Cochrane Database of Systematic Reviews 2002,

Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children

Comparison 1. Reduced osmolarity ORS compared to WHO standard ORS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Need for unscheduled intravenous fluid infusion	11	1996	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.45, 0.79]
2 Stool output	11	1776	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.33, -0.14]
3 Episode of vomiting during rehydration	6	1305	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.55, 0.92]
4 Presence of hyponatremia after rehydration	6	1120	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.93, 2.24]
5 Need for unscheduled intravenous fluid infusion (sensitivity analysis)	7	1688	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.46, 0.82]
6 Stool output (sensitivity analysis)	6	1550	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.31, -0.11]

Authors' conclusions

In children admitted to hospital with diarrhoea, reduced osmolarity ORS when compared to WHO standard ORS is associated with fewer unscheduled intravenous fluid infusions, lower stool volume post randomization, and less vomiting. No additional risk of developing hyponatraemia when compared with WHO standard ORS was detected.

Cochrane Database of Systematic Reviews 2002,

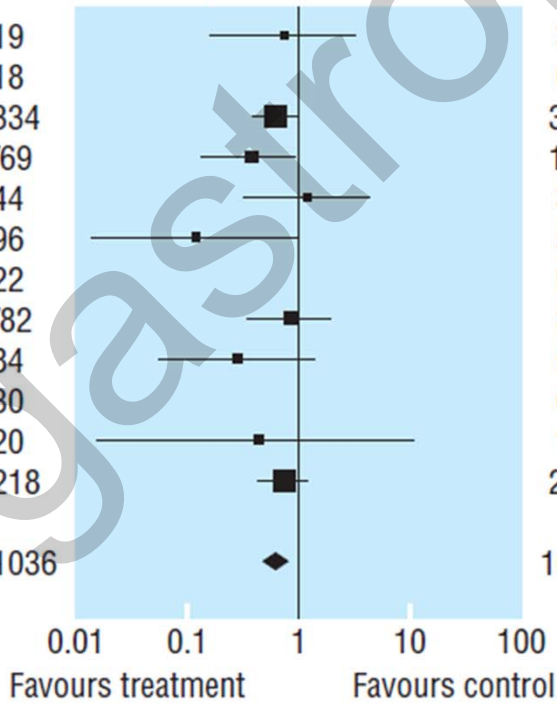
Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review

- To compare reduced osmolarity ORS with standard WHO ORS in children with acute diarrhea
- 15 RCTs (2397 patients)
- Primary outcome: unscheduled intravenous infusion
- Secondary outcome: stool output, vomiting and hyponatremia

BMJ 2001;323:81-5

Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review

Study	Intervention n/N	Control n/N	Odds ratio (95% CI fixed)	Weight %	Odds ratio (95% CI fixed)
Bangladesh 1995a[11]	4/19	5/19		3.0	0.75 (0.17 to 3.36)
Bangladesh 1996a[13]*	0/18	0/18		0.0	Not estimable
CHOICE 2001[14]	34/341	50/334		34.5	0.63 (0.40 to 1.00)
Colombia 2000[15]	7/71	16/69		11.1	0.36 (0.14 to 0.95)
Egypt 1996a[17]	6/45	5/44		3.3	1.20 (0.34 to 4.26)
Egypt 1996b[18]	1/94	8/96		5.9	0.12 (0.01 to 0.97)
India 1984a[19]*	0/22	0/22		0.0	Not estimable
India 2000b[21]	11/88	12/82		8.2	0.83 (0.35 to 2.01)
Mexico 1990a[22]	2/82	7/84		5.1	0.28 (0.06 to 1.37)
Panama 1982[23]*	0/33	0/30		0.0	Not estimable
USA 1982[23]	0/15	1/20		1.0	0.42 (0.02 to 11.03)
WHO 1995[24]	33/221	43/218		27.9	0.71 (0.43 to 1.18)
Total (95% CI)	98/1049	147/1036		100.0	0.61 (0.47 to 0.81)
χ^2=6.52, (df=8), z=3.50					



* No patients required intravenous infusion

Fig 1 Meta-analysis of unscheduled intravenous infusion among children randomised to reduced osmolarity and standard WHO rehydration solutions

BMJ 2001;323:81-5

Reduced osmolarity oral rehydration solution for treating dehydration due to diarrhoea in children: systematic review

- Conclusion
  - Fewer unscheduled IV infusion
    - Odd ratio 0.61, 95%CI 0.47 to 0.81
  - Lower stool output
    - Standardised mean difference in log scale -0.241, 95%CI -0.305 to -0.123
  - Less vomiting
    - Odd ratio 0.71, 95%CI 0.55 to 0.92
  - Non-significant hyponatremia
    - Odd ratio 1.45, 95%CI 0.93 to 2.26

BMJ 2001;323:81-5

Racecadotril

- Pure antisecretory agent that exerts antidiarrheal effect
- Enkephalinase inhibitor
- Does not increase intestinal transit time
- Does not cross blood brain barrier

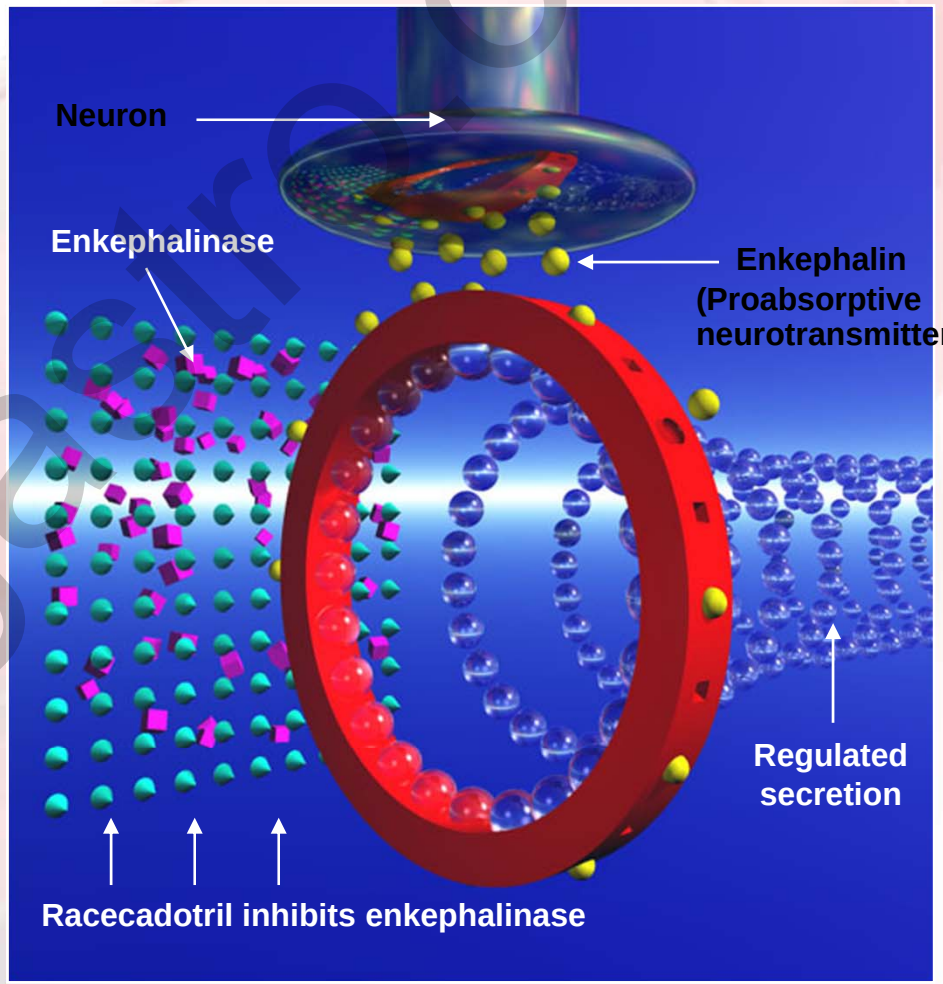
Aliment Pharmacol Ther 1999;13(Suppl.6):27-32

Mode of action of racecadotril

Inhibits enkephalinase activity

Protects enkephaline from inactivation

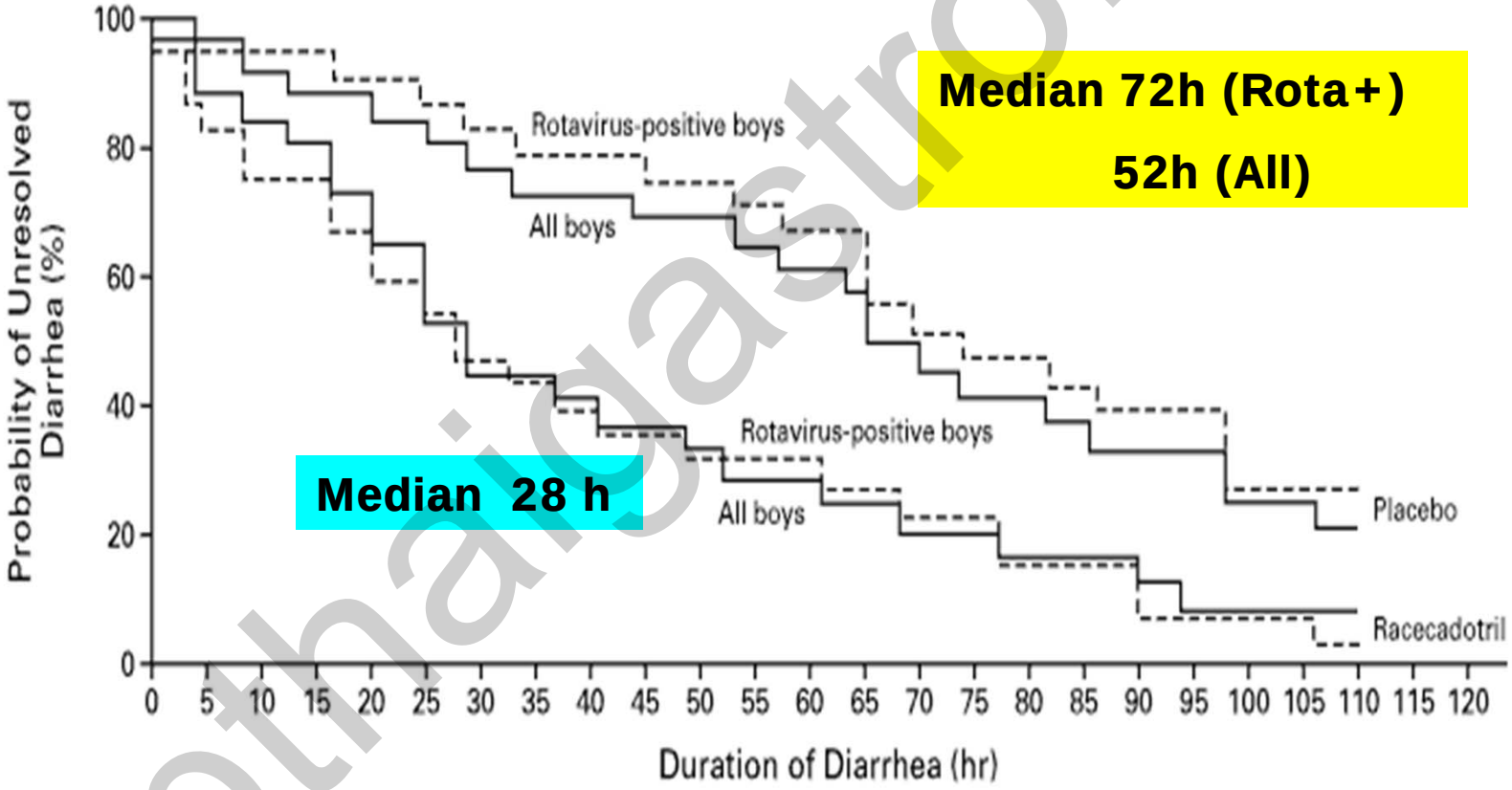
Reduces cytosolic cyclic AMP level and rapidly controls hypersecretion of water and electrolytes



Racecadotril

Salazar-Lindo's study : EFFICACY AND SAFETY OF RACECADOTRIL IN THE TREATMENT OF 135 PERUVIAN HOSPITALIZED MALE CHILDREN WITH ACUTE DIARRHOEA

Duration of diarrhea (actuarial curves)



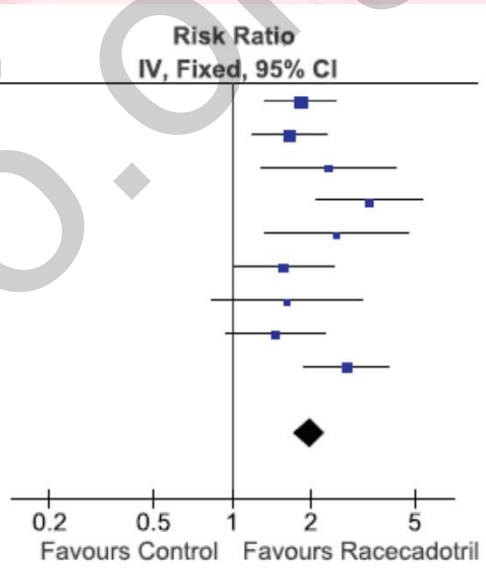
Salazar-Lindo E, Santisteban-Ponce J, Chea-Wood E and Guterriez M.
N Engl J Med 2000;343:463-467

Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio IV, Fixed, 95% CI
Cezard-01	61	89	31	83	20.8%	1.84 [1.34, 2.51]
SalazarLindo-00	47	68	28	67	19.3%	1.65 [1.20, 2.29]
Savitha-05	21	30	9	30	5.7%	2.33 [1.29, 4.23]
Gutierez1-10	60	135	18	135	9.2%	3.33 [2.08, 5.33]
Cojocaru-02	27	81	11	83	5.1%	2.52 [1.34, 4.73]
Santos-09	35	88	23	91	10.6%	1.57 [1.02, 2.44]
Alvarez-09	19	84	12	86	4.7%	1.62 [0.84, 3.13]
Melendez-07	19	25	13	25	10.6%	1.46 [0.94, 2.26]
Gutierez2-10	63	92	23	92	14.0%	2.74 [1.87, 4.01]
Total (95% CI)		**692**		**692**	**100.0%**	**1.98 [1.71, 2.28]**
Total events	352		168			

Heterogeneity: Chi² = 13.06, df = 8 (P = 0.11); I² = 39%

Test for overall effect: Z = 9.39 (P < 0.00001)



Conclusion: Dehydration level and Rotavirus at baseline are essential adjustments to compare treatments. As an adjunct to oral rehydration solution, racecadotril has a clinically relevant effect in reducing diarrhoea (duration, stool output and stool number), irrespective of baseline conditions (dehydration, Rotavirus or age), treatment conditions (inpatient or outpatient studies) or cultural environment.

Digestive and Liver Disease 43 (2011) 707-713

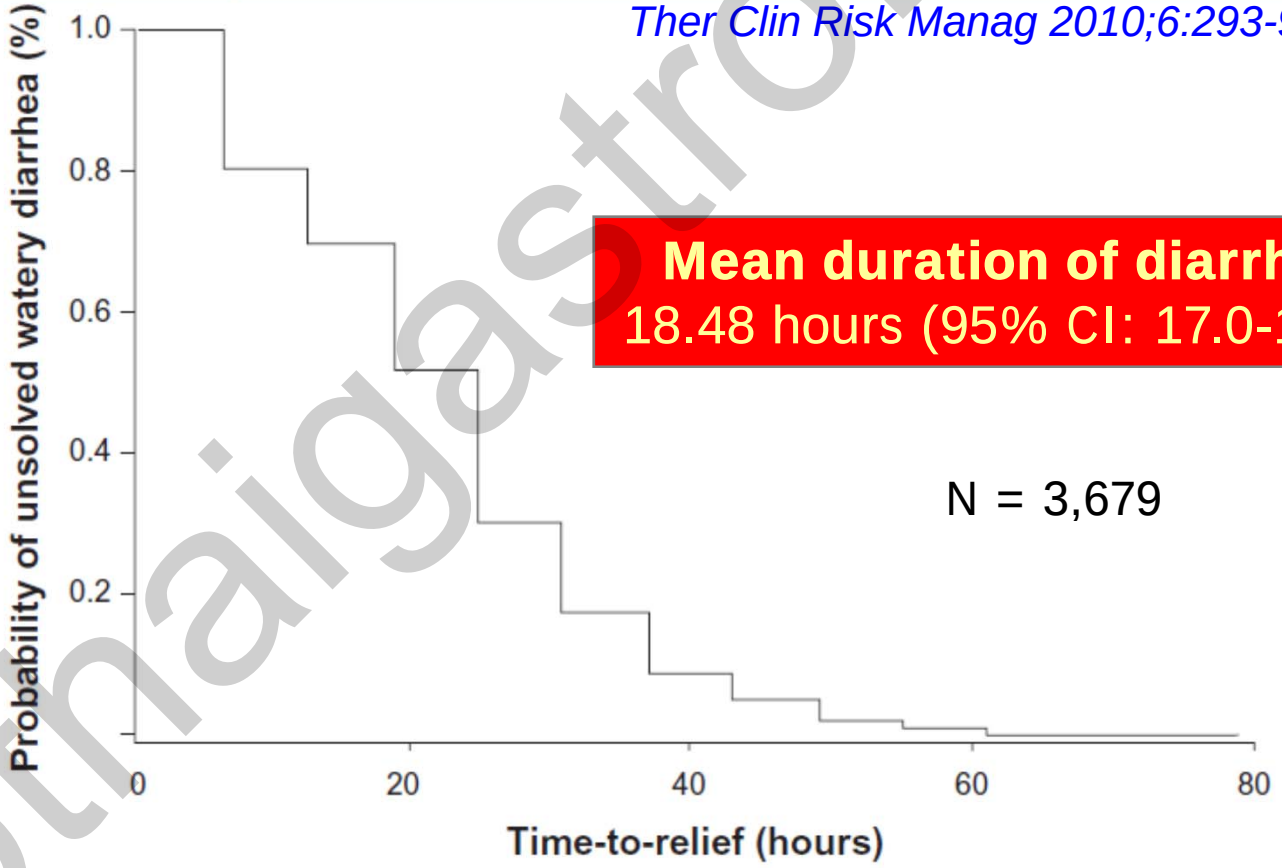
Analysis of factors influencing the overall effect of racecadotril on childhood acute diarrhea. Results from a real-world and post-authorization surveillance study in Venezuela

Ther Clin Risk Manag 2010;6:293-9

- Open-label, noncontrolled, prospective, multicenter, observational study
- September-December 2005, January-April 2006
- Age: 3 months – 12 years old
- Treatment: Rehydration therapy + Racecadotril 1.5 mg/kg/dose
- 3,679 patients completed the data
- Approximately 83% had moderate-to-severe diarrhea (≥ 5/day)

Analysis of factors influencing the overall effect of racecadotril on childhood acute diarrhea. Results from a real-world and post-authorization surveillance study in Venezuela

Ther Clin Risk Manag 2010;6:293-9



Mean duration of diarrhea
18.48 hours (95% CI: 17.0-19.0)

N = 3,679

Figure 1 Rates of recovery over time in children with acute watery diarrhea after racecadotril treatment. n = 3.679.

Probiotics

- Live microorganisms that, when administered in adequate amounts, confer a beneficial effect on the health of the host

Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food, Canada. 2002.

Action of Probiotics

- Regulation of intestinal microbial homeostasis
- Suppress growth of pathogens
- Block epithelial attachment or invasion by pathogens
- Enhance mucosal function
- Modulate host immune response

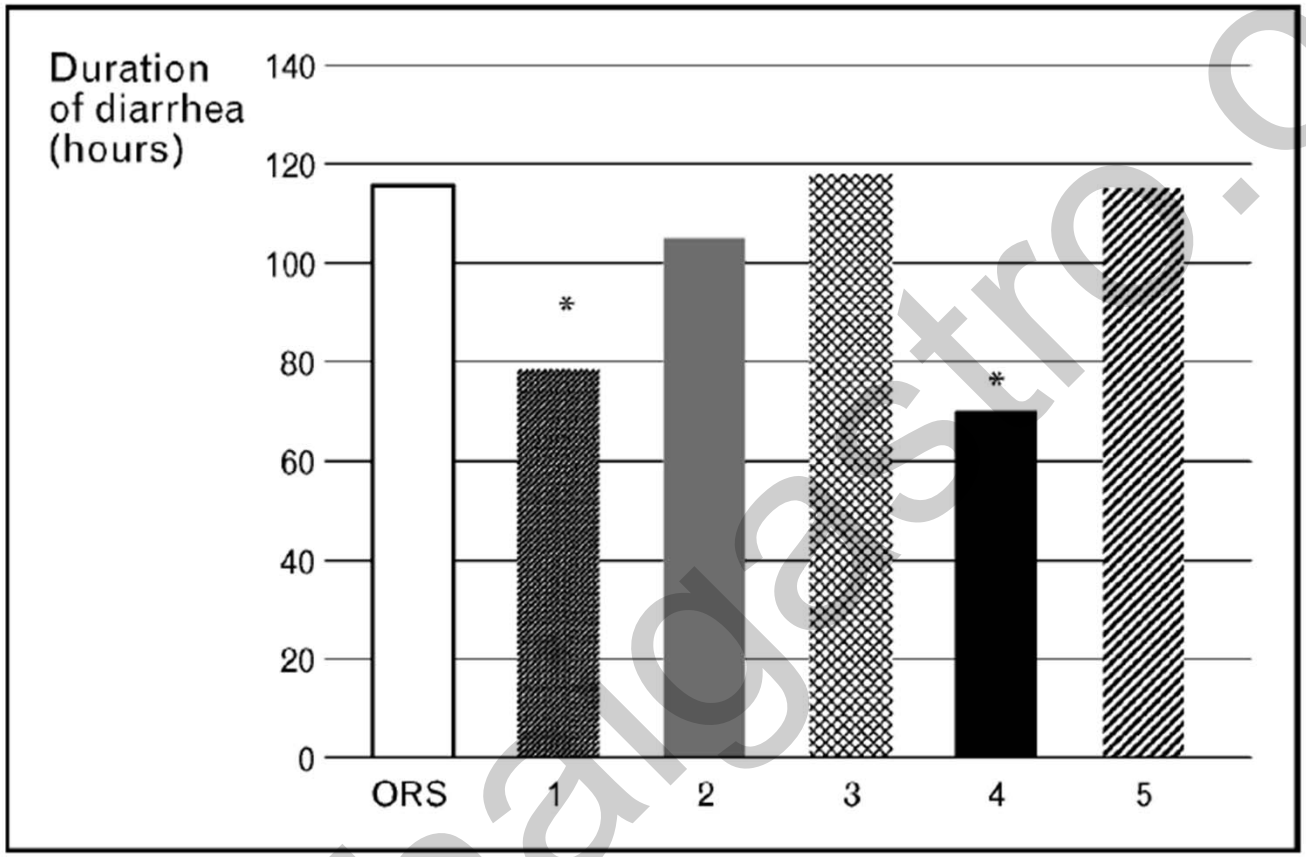
Recommendations for Probiotic Use-2011 Update

TABLE 1. Recommendations for Probiotic Use—Update 2011

Clinical Condition	Effectiveness	Specific Strain of Organism and Strain References
Diarrhea		
Infectious childhood—treatment	A	*Saccharomyces boulardii*,[15] LGG,[16] *Lactobacillus reuteri* SD2112[17]
Prevention of infection	B	*S. boulardii*,[15] LGG[16]
Prevention of AAD	A	*S. boulardii*.[19] LGG,[20] combination of *Lactobacillus casei* DN114 G01, *Lactobacillus bulgaricus*, snf *Saccharomyces thermophilus*[21]
Prevention of recurrent CDAD	B/C	*S. boulardii*,[11] LGG,[22] bacteriotherapy[14]
Prevention of CDAD	B/C	LGG,[11] *S. boulardii*[22]

J Clin Gastroenterol 2011;45:S168–S171

Figure 1 Effects of different probiotic strains on the duration of acute diarrhea in children



*=$P < 0.001$ compared with oral rehydration solution alone (Mann–

ORS (n=92)

1. *LGG* (100)
2. *S. boulardii* (91)
3. *B. clausii* (100)
4. *Bacterial mix* (97)
5. *E. faecium* (91)

BMJ 2007;335:340

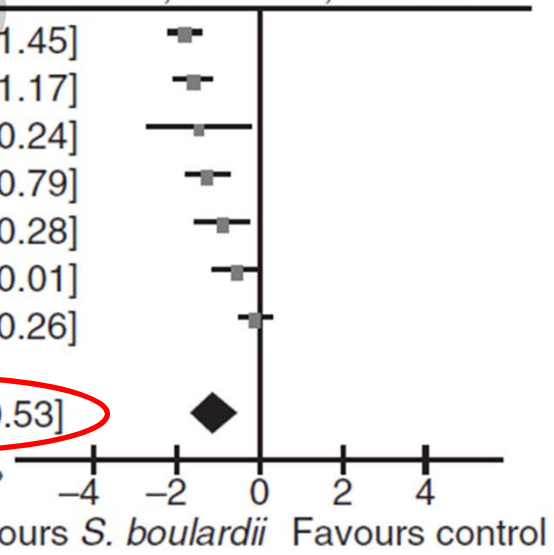
Curr Opin Gastroenterol 2008;25:18-23

Saccharomyces boulardii for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kurugol	2	1.1	100	3.8	1.4	100	15.9%	−1.80 [−2.15, −1.45]
Htwe	3.08	0.95	50	4.68	1.23	50	15.4%	−1.60 [−2.03, −1.17]
Villarruel	4.7	1.94	35	6.16	3.2	37	9.4%	−1.46 [−2.68, −0.24]
Billoo	3.56	1.01	50	4.82	1.38	50	15.1%	−1.26 [−1.73, −0.79]
Hafeez	3.6	1.6	51	4.5	1.6	50	14.0%	−0.90 [−1.52, −0.28]
Vandenplas	2.24	1.6	93	2.8	2.19	95	14.6%	−0.56 [−1.11, −0.01]
Canani	4.59	1.35	91	4.7	1.17	92	15.8%	−0.11 [−0.48, 0.26]
Total (95% CI)			470			474	100.0%	−1.08 [−1.64, -0.53]

Heterogeneity: $Tau^2 = 0.47$; $Chi^2 = 53.61$, df = 6 ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: $Z = 3.82$ ($P = 0.0001$)



Aliment Pharmacol Ther 2009;30(9):960-1

Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children

- 7 RCTs (876 infants)
- Significant reduction in diarrhea duration
  - Weighted mean difference, WMD -1.1 days (95%CI -1.9 to -0.3)
  - Rotavirus, WMD -2.1 days (-3.6 to -0.6)

Aliment Pharmacol Ther 2007; 25:871–881

Cost-effectiveness of Probiotic Combination (Lactobacillus acidophilus plus Bifidobacterium bifidum) in Treating Acute Childhood Diarrhea in Hospitalized Patients

Department of Pediatrics, Phramongkutklao Hospital

- Double-blinded, randomized, placebo-controlled trial
- Children 3-72 months of age hospitalized into Phramongkutklao hospital with acute diarrhea
- Hospital charges, length of hospitalization, duration of diarrhea were compared

N. Phavichitr et al.

Baseline characteristic

	L. acidophilus+ B. bifidum N=53	Placebo N=53	P-value
Age (mo) Median (range)	15 (4-72)	19 (6-64)	0.185
Sex (M:F)	31:22	28:25	0.558
BW	9.4 (6.5-23.3)	10.2 (6.2-20)	0.251
Duration of diarrhea (d)	2 (0-7)	2 (0-6)	0.606
No. of diarrhea in last 24 h	6 (3-25)	6 (1-20)	0.799
Rotavirus positive	21 (39.6%)	15 (29.4%)	0.274

Result

	L. acidophilus+ B. bifidum N=53	Placebo N=53	P-value
Length of hopitalization(d) Median (min-max)	2(1-6)	3(1-8)	0.049*
Duration of illness (d) Median (min-max)	4(2-11)	5(2-12)	0.068
Hospital charges including cost of study drug (baht) Median (min-max)	4,418.75 (2,0345.5-10,019)	4778.75 (1,877-10,575.25)	0.342
Hospital charges plus drug cost plus parental income loss (baht) Median (min-max)	6,800.33 (2,301.17-20,659.42)	7,970.92 (2,994-24,026.75)	0.177

Cost-effectiveness of Probiotic Combination (Lactobacillus acidophilus plus Bifidobacterium bifidum) in Treating Acute Childhood Diarrhea in Hospitalized Patients

Department of Pediatrics, Phramongkutklao Hospital

- Authors' conclusions: Probiotic combination *Lactobacillus acidophilus/Bifidobacterium bifidum* could shorten duration of hospitalization for one day. Although there was no difference in the cost of treatment, the probiotic therapy did not increase the total expenses.

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Adsorbents

- Smectite
  - natural hydrated aluminomagnesium silicate
  - Bind endo-and exotoxins, bacteria and rotavirus
  - Restored barrier property of intestinal cell
  - Modified the activity of bile salt and the physical properties of gastric mucus
  - Increased water and electrolyte absorption

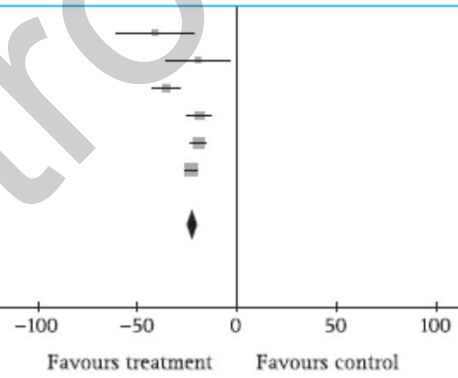
Meta-analysis: Smectite in the treatment of acute infectious diarrhoea in children

H. SZAJEWSKA*, P. DZIECHCIARZ* & J. MRUKOWICZ†

Table 3. Smectite vs. control [mean duration of diarrhoea (h)]

Study or sub category	N	Smectite mean (S.D.)	N	Control mean (S.D.)	WMD (fixed; 95% CI)	WMD (fixed; 95% CI)
Vivatvakin	32	43.30(25.10)	30	84.70(48.50)		-41.40 (-60.81 to -21.99)
Narkeviciute	28	42.30(24.70)	26	61.80(33.90)		-19.50 (-35.42 to -3.58)
Zong	20	48.72(5.16)	10	84.48(10.80)		-35.76 (-42.83 to -28.69)
Madkour	45	54.10(15.80)	45	72.92(13.30)		-18.82 (-24.85 to -12.79)
Lachaux	17	42.00(4.70)	19	61.30(7.10)		-19.30 (-23.20 to -15.40)
Guarino	398	96.00(21.00)	406	119.00(23.00)		-23.00 (-26.04 to -19.96)
Total (95% CI)	540		536			-22.70 (-24.80 to -20.61)

Test for heterogeneity: $\chi^2 = 21.40$, d.f. = 5 ($P = 0.0007$), $I^2 = 76.6\%$
Test for overall effect: $Z = 21.24$ ($P < 0.00001$)



Conclusions

Smectite may be a useful adjunct to rehydration therapy in treating acute paediatric gastroenteritis. However, the results of this meta-analysis should be interpreted with caution as most of the included studies had important limitations. Cost-effectiveness analyses should be undertaken before routine pharmacological therapy with smectite is recommended.

Aliment Pharmacol Ther 2006;23:217-27

Antiemetics

- Ondansetron
  - Potent and selective serotonin $5HT_3$- receptor antagonist
  - Rapidly absorbed after oral intake
  - Safe and effective in preventing chemotherapy- and radiation-induced vomiting
  - Very low risk of adverse effects
  - The most common side effect is diarrhea

Emergency department use of oral ondansetron for acute gastroenteritis-related vomiting in infants and children

A Cheng; Cana

Canadian Paediatric Society

Francais en page 180

RECOMMENDATIONS

Oral ondansetron therapy, as a single dose, should be considered for infants and children six months to 12 years of age who present to the ED with vomiting related to suspected acute gastroenteritis, and who have mild to moderate dehydration or who have failed oral rehydration therapy. Because the most common side effect of ondansetron is diarrhea, its use is not routinely recommended in children with gastroenteritis whose predominant symptom is moderate to severe diarrhea. A reasonable weight-based oral dosing regimen for infants and children is the following:

- 8 kg to 15 kg: 2 mg
- 15 kg to 30 kg: 4 mg
- Greater than 30 kg: 6 mg to 8 mg

TABLE 1
Clinical trials: Us

Study, year	Patie n	ent, RR (95% CI) Hospital admission
Freedman et al (20), 2006	21	0.80 (0.22–2.90)
Roslund et al (21), 2008	10	0.46 (0.12–1.79)
Ramsook et al (22), 2002	14	0.17 (0.04–0.78)

ED Emergency departi

Paediatr Child Health 2011;16(3):177-179.

[Intervention Review]

Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents

- Cochrane analysis
- Pooled data from 3 RCTs comparing oral ondansetron with placebo
  - Reduction in immediate hospital admission rate (RR 0.40, NNT 17, 95% CI 10 to 100)
  - Reduction in IV rehydration rate (RR 0.41, NNT 5, 95% CI 4 to 8)
  - Increase proportion of patients with cessation of vomiting (RR 1.34, NNT 5, 95% CI 3 to 7)

Cochrane Database Syst Rev 2011 Sep 7;(9):CD005506

Conclusions

- Effective therapy in acute diarrhea
  - Reduced osmolarity ORS
  - Antisecretory drug: Racecadotril
  - Probiotics: *S. boulardii, Lactobacillus*
  - Adsorbents: Smectite
  - Antiemetic drug: Ondansetron