Drugs Used in Acute Diarrhea: Cons

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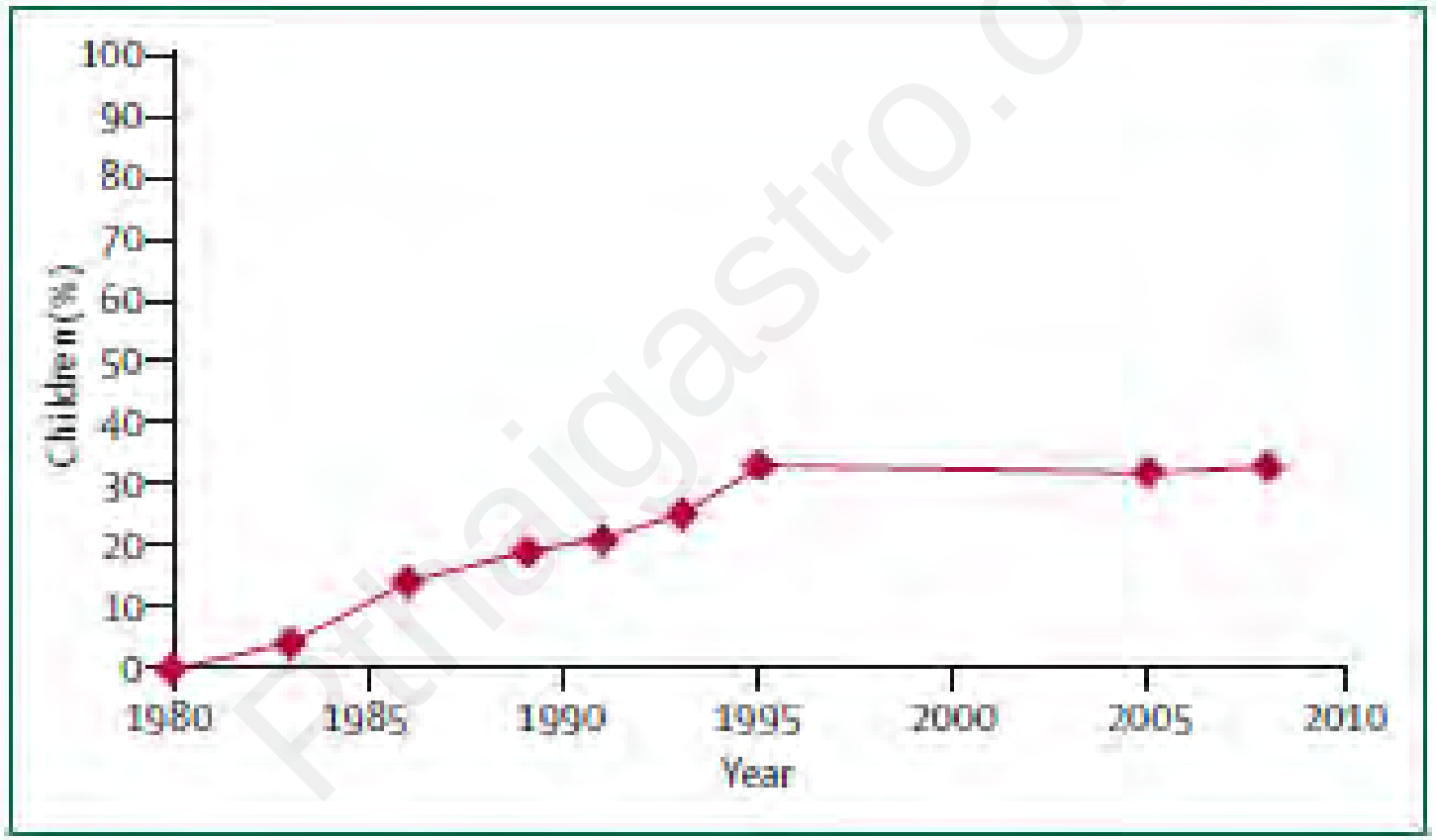
Optimistic

Pessimistic

Global percentage of children <5 y with diarrhoea who received ORS



Santosham M, et al. *Lancet* 2010; 376: 63-7.

Current clinical practice problems

- Only 31% of doctors prescribed ORS for diarrhoea in a study in India.
- Doctors might prescribe medication because the original ORS did not shorten the duration of illness or reduce the stool output from diarrhoea, and thus would not be seen as an effective treatment.
- As a result, parents demand additional medications, especially from private practitioners.

Santosham M, et al. *Lancet* 2010; 376: 63-7.

Drugs in the prescriptions for acute diarrhoea in Ujjain, India (n = 843)

	Number	Percentage	Percentage range between clusters[a]
ORS	487	58	19-99%
ORS with zinc	188	22	0-53%
ORS with zinc and antibiotics	88	10	0-41%
Zinc only	228	27	0-53%
Antibiotics	602	71	8-100%
Probiotics	574	68	
Racecadotril	160	19	
Miscellaneous (for fever, pain in stomach, vomiting)	589	69	

Pathak D, et al. BMC Infectious Diseases 2011; 11: 32.

Oral Rehydration Solution

Oral Rehydration Solution

Among adults with cholera, clinical outcomes did not differ among those treated with reduced-osmolarity ORS compared with standard ORS, although there was a risk of transient asymptomatic hyponatremia.

Further monitoring, including postmarketing surveillance studies, were strongly encouraged to assess better any risk of symptomatic hyponatremia in cholera-endemic parts of the world.

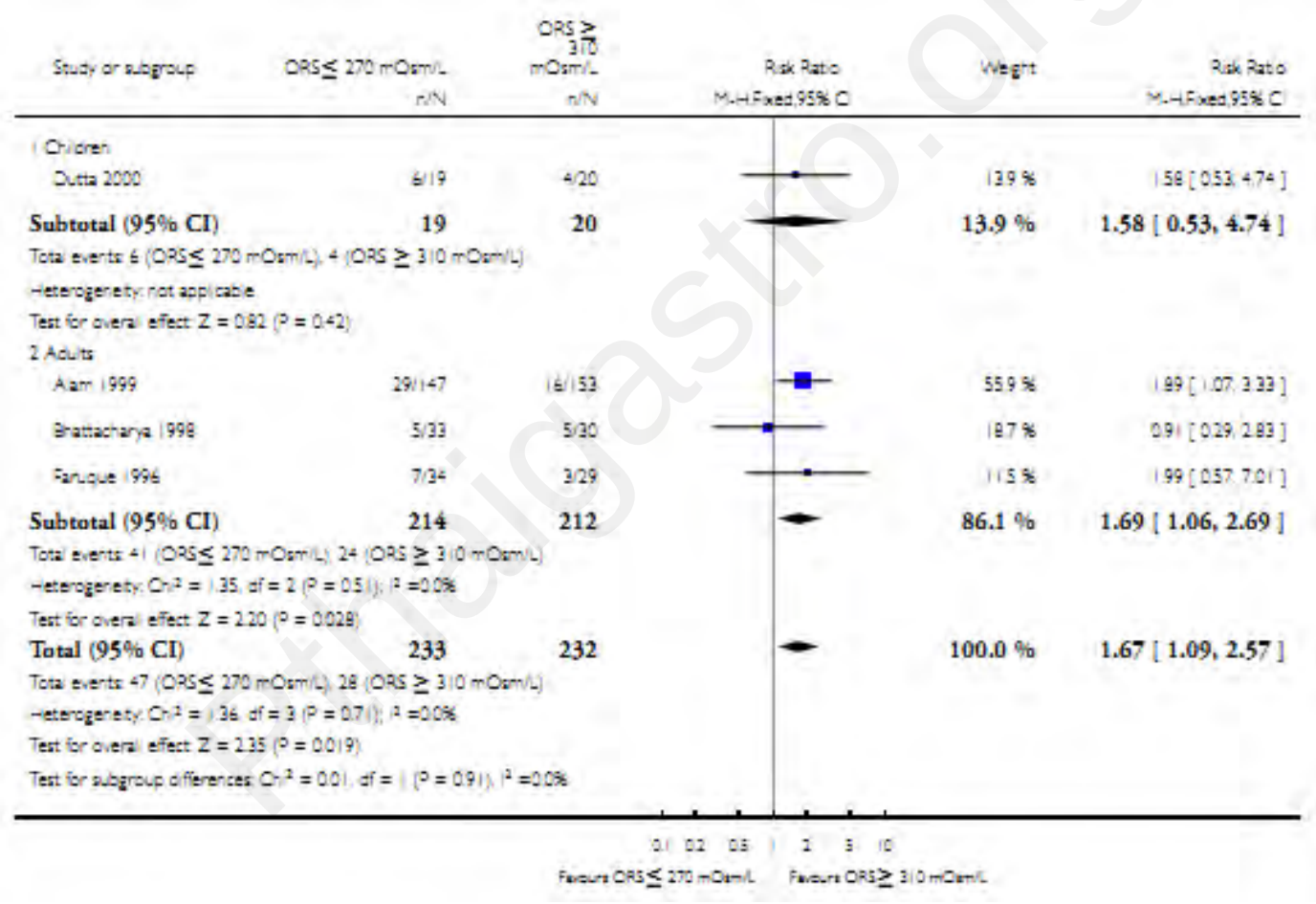
WHO & UNICEF 2001

ORS for treating cholera: ≤ 270 mOsm/L vs ≥ 310 mOsm/L

- **MAIN RESULTS: For glucose-based ORS, seven trials (718 participants) met the inclusion criteria.**
- **Biochemical hyponatremia (blood sodium levels < 130 mmol/L) was more common with ORS ≤ 270 (RR 1.67, CI 1.09 to 2.57; 465 participants, four trials)**

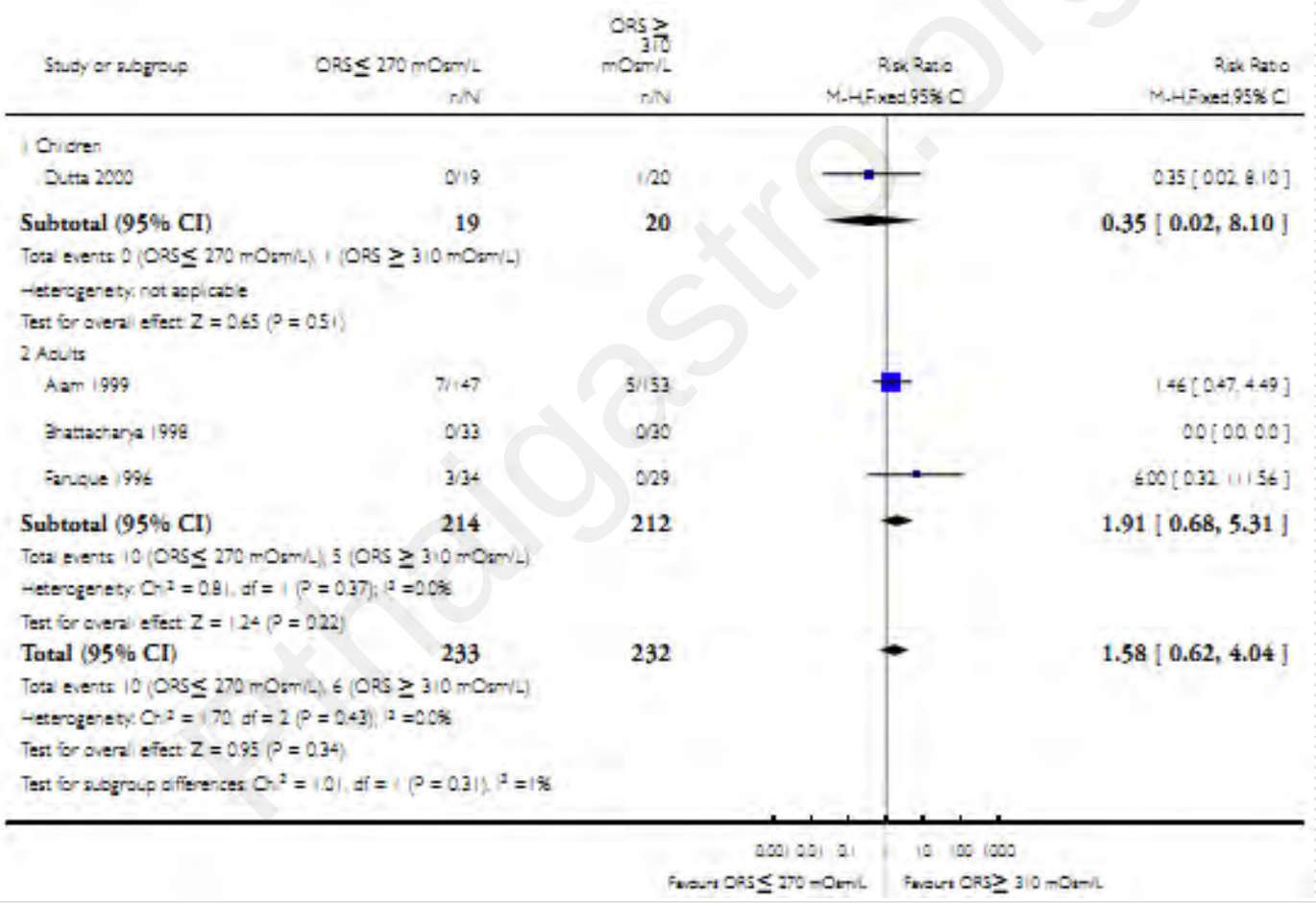
Musekiwa A, et al. Cochrane Database Syst Rev 2011, Issue 12.

Biochemical hyponatremia (serum sodium < 130 mmol/L)



Musekiwa A, et al. Cochrane Database Syst Rev 2011, Issue 12.

Severe biochemical hyponatremia (serum sodium < 125 mmol/L)



Musekiwa A, et al. Cochrane Database Syst Rev 2011, Issue 12.

ORS for treating cholera: ≤ 270 mOsm/L vs ≥ 310 mOsm/L

- **Authors' conclusion:** Although this risk does not appear to be associated with any serious consequences, the total patient experience in existing trials is small. Under wider practice conditions, especially where patient monitoring is difficult, caution is warranted.

Musekiwa A, et al. Cochrane Database Syst Rev 2011, Issue 12.

Racecadotril

Racecadotril

- There is evidence in favor of the use of racecadotril over placebo or no intervention to reduce the stool output in children with AGE. However, this evidence is based mainly on in-patient data, and does not take into account safety concerns that can be resolved either in studies involving large cohorts of children or in postmarketing surveillance evaluation, which is mandatory before therapy with racecadotril can be recommended.

Racecadotril as Outpatient Treatment

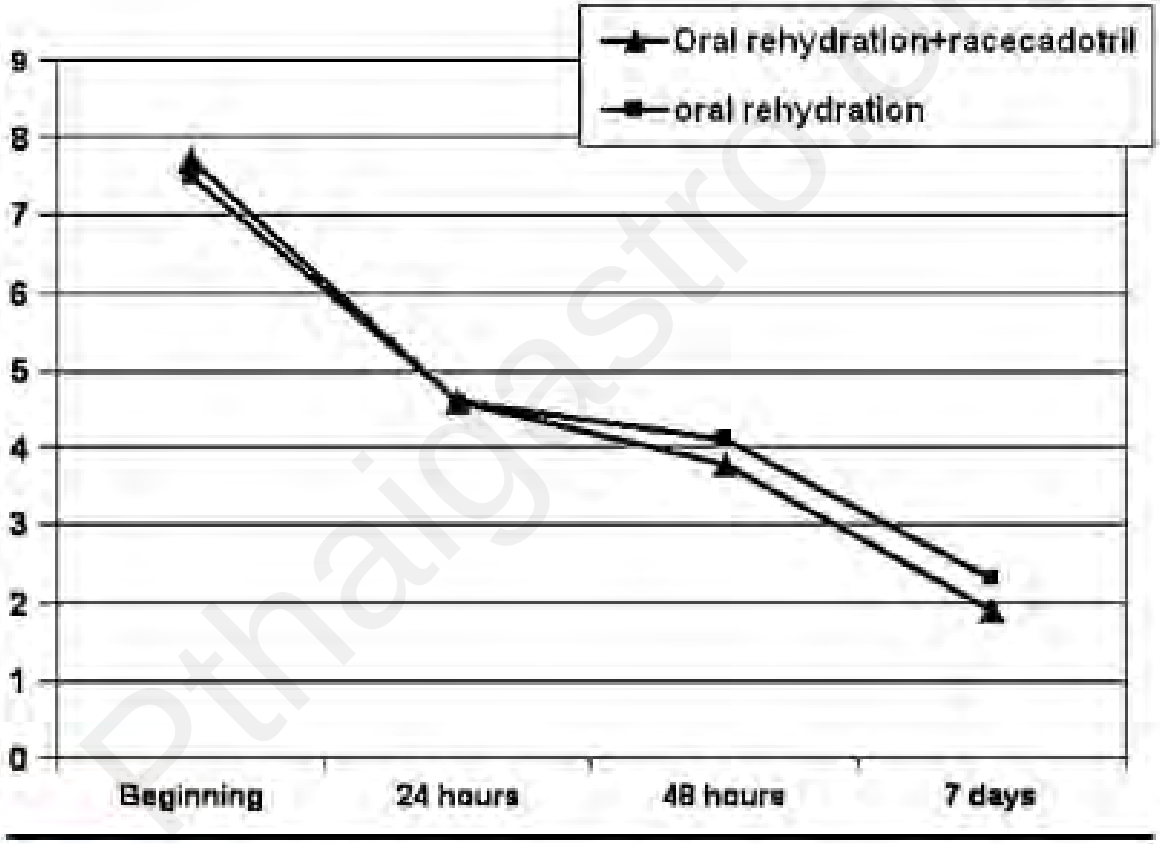


Figure 1. Evolution in number of bowel movements (ITT).

Santos M, et al. J Pediatr 2009;155:62-7.

Racecadotril as Outpatient Treatment

- No differences were found in the average duration of gastroenteritis (4.7 ± 2.2 days in the OR group, 4.0 ± 2.1 days in the OR+R group; P = 0.15).

Santos M, et al. J Pediatr 2009;155:62-7.

Racecadotril: an individual patient data meta-analysis

- Baseline dehydration level and Rotavirus were found as two essential predictors influencing the outcomes.
- Racecadotril safety was briefly reported in this analysis, and investigated elsewhere
- The economic utility of this compound remains to be demonstrated

Nine randomised clinical trials (n = 1384)

Lehert P, et al. Digest Liver Dis 2011; 43: 707–13.

Probiotics

Probiotics for treating acute infectious diarrhoea

- The benefit is strain-dependent
- Seem to be more effective when given early in the course of diarrhea
- Most helpful for otherwise healthy infants and young children with watery diarrhea secondary to viral gastroenteritis but not invasive bacterial infections

AAP-Clinical Report: Probiotics and Prebiotics in Pediatrics

Thomas DW, et al. Pediatrics 2010; 126: 1217–31.

Probiotics for treating acute infectious diarrhoea

- **The marked clinical variability among studies complicates meta-analysis and, therefore, weakens the evidence base to inform clinical practice. In particular, variability in the definition of diarrhoeal episodes results in misclassification and impairs the comparability of the findings from different studies**

Sixty-three studies (n = 8014)

Allen SJ, et al. Evid-Based Child Health 2011;6:1894–2021.

Probiotics for treating acute infectious diarrhoea

- More large, well-designed studies are needed of specific probiotic regimens in specific settings.
- In future research, the standardization of definitions of acute diarrhoea, treatment regimens, inclusion criteria and outcome measures are needed to facilitate comparison of results across studies.

Allen SJ, et al. Evid-Based Child Health 2011;6:1894–2021.

Probiotics for treating acute infectious diarrhoea

- **AUTHORS' CONCLUSIONS:**
  Used alongside rehydration therapy, probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhoea. However, more research is needed to guide the use of particular probiotic regimens in specific patient groups.

Allen SJ, et al. Evid-Based Child Health 2011;6:1894–2021.

Research questions for Probiotics in infants and children

- The preferred microbial dose and species
- The optimal duration of probiotic administration
- The specific clinical diseases
- The long-term impact on the gut micro-flora in children is unknown

AAP-Clinical Report: Probiotics and Prebiotics in Pediatrics

Thomas DW, et al. Pediatrics 2010; 126: 1217–31.

Safety of Probiotics in infants and children

- Probiotics should not be given to children who are seriously or chronically ill until the safety of administration has been established.
- Patients at risk would be those who are immunocompromised, including ill preterm neonates, and/or children who have intravenous catheters or other indwelling medical devices.

AAP-Clinical Report: Probiotics and Prebiotics in Pediatrics

Thomas DW, et al. Pediatrics 2010; 126: 1217–31.

Systemic infections

- The risk of developing bacteremia from Lactobacillus <1 per 1 million users[1]
- The risk of developing fungemia from *S. boulardii* –1 per 5.6 million users[1]
  - estimated to be lower in healthy individuals[2]
- No reports of bifidobacterium sepsis associated with the use of probiotics in healthy individuals[3]

1. Boriello, et al. ClinInfect Dis 2003; 36(6): 775-80.
2. Karpa. Ann Pharmacother 2007; 41(7): 1284-7.
3. Boyle et al. Am J ClinNutr 2006; 83(6): 1256-64.

Smectite

Smectite

- Its mechanisms of action are not yet fully understood, but are probably multiple
- Many studies have focused only on the water-binding effect of clays and subsequent modification of stool form

Dupont C, et al. Pediatr Drugs 2009; 11: 89-99.

Smectite

- **Smectite reduces inflammation, modifies mucus rhéologie properties, inhibits mucolysis, and adsorbs bacteria, bacterial enterotoxins, viruses and other potentially diarrheogenic substances.**

Dupont C, et al. Pediatr Drugs 2009; 11: 89-99.

Smectite

- It can be administered as an adjunct to ORT without affecting its absorption or efficacy, but antibacterial agents need to be administered at least 60-90 minutes before or after smectite.
- Studies to determine the cost effectiveness of smectite in combination with ORT would also be useful.

Dupont C, et al. Pediatr Drugs 2009; 11: 89-99.

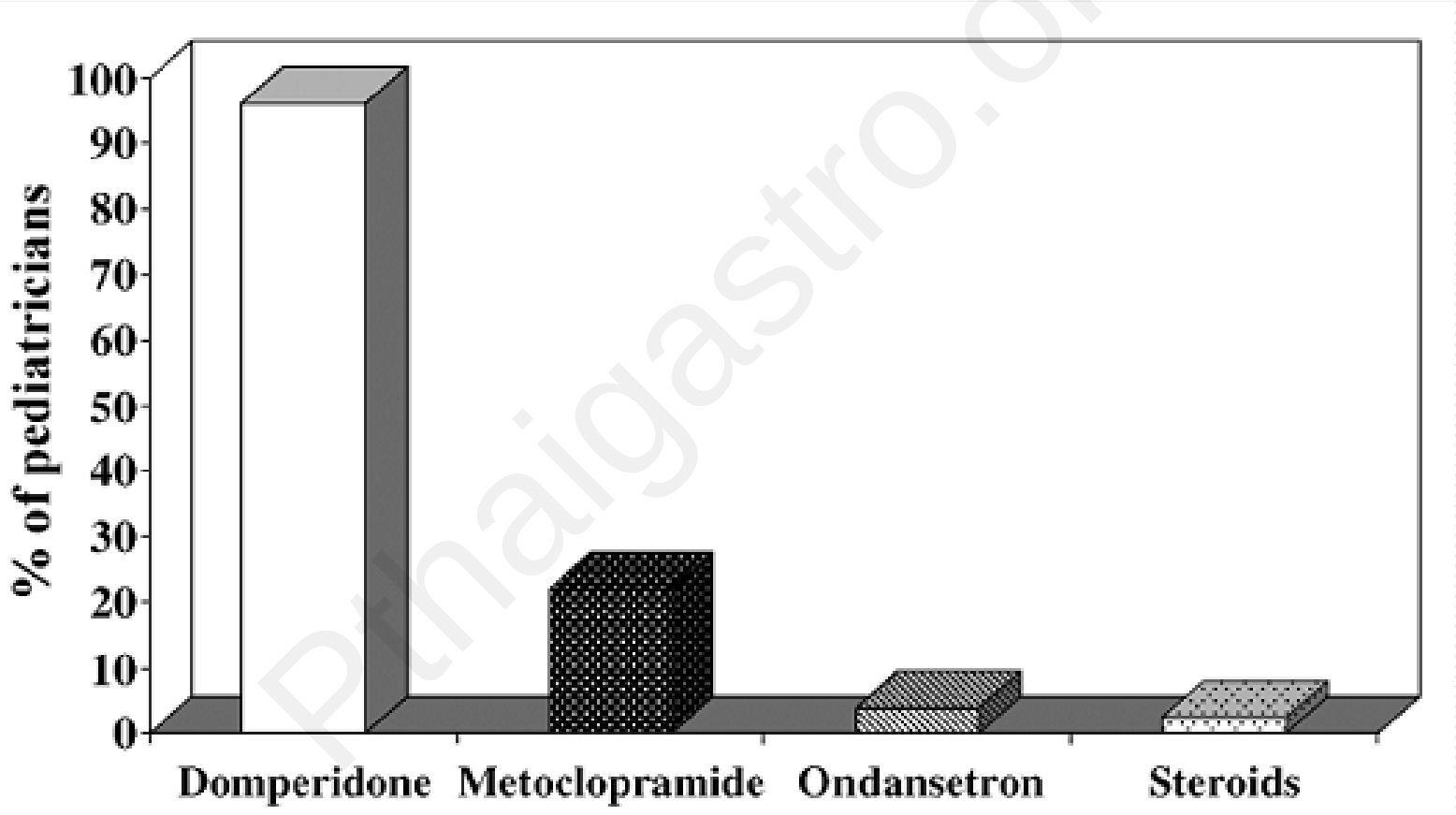
Antiemetics

Antiemetics

- **Antiemetics are not included for treatment of vomiting associated with acute gastroenteritis (AGE) in children by standard guidelines.**

AAP 1996, WHO & UNICEF 2001, & ESPGHAN-ESPID 2008

Off-label used of antiemetics



Albano F, et al. *JPGN* 2006; 43: 402-4.

Domperidone with ORT in the Treatment of Pediatric Acute Gastroenteritis in Japan

- A total of 56 children were eligible; 24 received ORT alone, and 32 received ORT and prescribed domperidone suppository
- 27.3% of children in the ORT group vomited as compared with 20.7% of children in the ORT and domperidone group (P = 0.41)

Kita F, et al. Asia Pac J Public Health. 2012; Jan 10. [Epub ahead of print]

Dimenhydrinate in Children With Infectious Gastroenteritis

- The mean number of vomiting episodes between randomization and follow-up visit was 0.64 in the dimenhydrinate group and 1.36 in the placebo group ($p=0.001$).
- In total, 69.6% of the children in the dimenhydrinate group versus 47.4% in the placebo group were free of vomiting between randomization and the follow-up visit ($p < 0.001$).

Uhlig U, et al. Pediatrics 2009;124:e622–e632.

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

- These were noted in all treatment groups. All patients in the study experienced at least one episode of diarrhea but compared with placebo there were significantly more episodes of diarrhea in the ondansetron (P = 0. 013) and metoclopramide (P = 0.004) groups in the first 24 hours, although there was no significant difference between these two groups.

Fedorowicz Z, et al. Cochrane Database Syst Rev 2011, Issue 9.

Adverse effect of Ondansetron & metoclopramide

- The increased incidence of diarrhea noted with both ondansetron and metoclopramide was considered to be a result of retention of fluids and toxins that would otherwise have been eliminated through the process of vomiting.

Zinc supplementation

UNICEF and WHO recommend zinc supplementation (10 mg < 6 mo, and 20 mg in older infant and children for 10-14 days) as a universal treatment for children with diarrhea.

Santosham M, et al. *Lancet* 2010; 376: 63-7.

Oral Zinc for the Treatment of Acute Gastroenteritis in Polish Children

Table II. Outcome measures

Outcome measure	Placebo n = 72	Zinc n = 69	Effect size (95% CI)	*P* value*
Diarrhea duration in hours, median (range)	39 (12-196)	58 (12-187)	Median difference 4 (-5-18)	.33
Stool frequency (n/day), median (range)				
Day 1	4 (0-38)	5 (0-20)	1 (0-2)	.13
Day 2	3 (0-14)	3 (0-17)	0 (0-1)	.30
Day 3	2 (0-13)	2 (0-10)	0 (0-1)	.31
Vomiting frequency (n/day), median (range)				
Day 1	0 (0-4)	0 (0-7)	0 (0-0)	.68
Day 2	0 (0-3)	0 (0-4)	0 (0-0)	.37
Day 3	0 (0-10)	0 (0-5)	0 (0-0)	.91
Total intravenous fluid intake (mL/kg), median (range)	72 (0-318)	73 (0-425)	0 (-33-12)	.48
Diarrheal episodes lasting >7 days, n (%)	3 (4.2)	1 (1.4)	Relative risk 0.35 (0.04-3.26)	.61

Patro B, et al. J Pediatr 2010;157:984-8

Antibiotic therapy

Antibiotic therapy is not needed in most case of AGE and may induce a carrier status in case of *Salmonella* infection. Antibiotic treatment is effective mainly in shigellosis, cholera, and in the early stage of *Campylobacter* infection.

Antibiotics may do harm

- EHEC -bacteria die release toxin increase risk to HUS.
- Salmonella -prolong carrier.
- Rotavirus -prolong recovery.
- *V. cholerae* -drug resistance

Don't Mix Up Your Medication

Ladies, what happens if you confuse your Valium with your birth control pills?

You end up with 12 kids, but you don't really care.

Thank you!