Review article: the management of acute gastroenteritis in children

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SUMMARY

Background
In 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Disease (ESPID) developed evidence-based guidelines for the management of acute gastroenteritis (AGE) in children in Europe.

Aim
To summarise data published subsequently to the ESPGHAN/ESPID guidelines.

Methods
MEDLINE and The Cochrane Library were searched in August 2012 for randomised controlled trials (RCTs) or their meta-analyses published after 2008.

Results
Efforts to improve the taste and/or efficacy of oral rehydration solution (ORS) continue, and some interventions are promising. While standard (over 24 h) nasogastric rehydration is still being used, new evidence confirms that rapid (over 4 h) rehydration is also effective. For intravenous rehydration, new evidence is available regarding rapid or ultrarapid and large-volume vs. standard-volume rehydration; as the new evidence is not consistent, until more data are available, the administration of 20 mL/kg seems appropriate. Convincing evidence has accumulated showing that ondansetron reduces the risk for vomiting; however, a clearance on safety in children is needed. New evidence has reconfirmed that in Europe, where zinc deficiency is rare, there is no benefit from the use of zinc. New data, although mainly from outside of Europe, have reconfirmed that either smectite or racecadotril is an effective adjunctive therapy to oral rehydration. There is a clear effect of using certain probiotics, such as *Lactobacillus* GG or *S. boulardii*.

Conclusions
The update of current ESPGHAN/ESPID recommendations is warranted.

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INTRODUCTION

Acute gastroenteritis (AGE), characterised by the sudden onset of diarrhoea with or without vomiting, is one of the most common infectious diseases of childhood. In Europe, it is estimated that the incidence of diarrhoea ranges from 0.5 to 1.9 episodes per child per year in children up to 3 years of age.[1] In low- and middle-income countries, while the incidence of acute diarrhoea has declined from 3.4 episodes/child year in 1990 to 2.9 episodes/child year in 2010, the incidence of AGE remains high, especially in infants aged 6–11 months (4.5 episodes/child year).[2] Moreover, worldwide diarrhoea remains one of the leading causes of mortality among children younger than 5 years.[3]

In 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Diseases (ESPID) developed evidence-based guidelines for the management of AGE for practitioners at all levels of health care – primary care physicians, paediatricians and family physicians – practising in Europe.[1] In addition, a number of national guidelines have been developed, although their quality varies.[4] Perhaps the best known among them are those developed by the National Institute for Health and Clinical Excellence (NICE).[5]

Both ESPGHAN/ESPID and the NICE guidelines largely agree on key issues in the management of AGE. Oral rehydration therapy with a hypotonic solution remains central to the management of AGE. Fast oral rehydration with rapid return to regular food is recommended. The routine use of special or diluted formulas is unjustified. Continuation of breastfeeding is strongly recommended. The guidelines recommend against the routine use of antibiotics in otherwise healthy children presenting with AGE. Regarding drugs, both sets of guidelines recommend against the use of antiemetics, but they strongly emphasise the need for further research. Compared with the NICE guidelines, the ESPGHAN/ESPID guidelines make a stronger recommendation for the use of probiotics for the management of AGE, particularly those with documented efficacy such as *Lactobacillus* GG and *Saccharomyces boulardii*. The ESPGHAN/ESPID guidelines state that treatment with racecadotril (an enkephalinase inhibitor) may be considered in the management of AGE. Both sets of guidelines state that there is evidence suggesting that smectite (a natural hydrated aluminomagnesium silicate that binds to digestive mucus and has the ability to bind endotoxins and exotoxins, bacteria and rotavirus) is an effective antidiarrhoeal agent, but only the ESPGHAN/ESPID guidelines recommend that the use of smectite may be considered in the management of AGE.

The objective of this review was to summarise the more recent data on the management of AGE published subsequently to the ESPGHAN/ESPID document, and to find out whether this added information justifies revision of the guidelines. We searched MEDLINE and The Cochrane Database of Systematic Reviews in August 2012 for randomised controlled trials (RCTs) or their meta-analyses (considered the best study design for answering questions about the effectiveness of an intervention) published in the last 5 years related to the management of AGE in the paediatric population. No limit was imposed regarding the language of publication. In particular, we searched for studies on the use of enteral (oral or nasogastric) and intravenous rehydration therapy, antiemetics and antidiarrhoeal drugs [such as probiotics, (dio)smectite, zinc, racecadotril] compared with placebo or no intervention in children (for summary of evidence, see Table 1). Studies related to the use of antimicrobials are not covered in this review. We focused primarily, although not exclusively, on studies performed in high-income populations. In the case of diarrhoeal diseases, consideration of the study location is important, as factors such as pathogens, access to clean water and sanitation, or comorbidities may have an impact on outcomes.

ORAL REHYDRATION THERAPY

Despite the proven efficacy of oral rehydration therapy, it remains underused.[6, 7] The main reasons for this are that an oral rehydration solution (ORS) neither reduces the frequency of bowel movements and fluid loss nor shortens the duration of illness, which decreases its acceptance. Moreover, the unpalatability of regular ORS (strong salty taste) also decreases its acceptance, although this is only an issue in infants and young children who are not dehydrated.

ORS with improved taste

The study by Freedman *et al.*[8] was a prospective, double-blind, randomised, 3-period, 3-treatment cross-over trial conducted in 66 children aged 5–10 years with concerns unrelated to the gastrointestinal tract. The aim of the study was to compare the palatability of 3 ORSs (i.e. Pedialyte and Pediatric Electrolyte, which both contain sucralose, and Enfalyte, which contains rice syrup solid). For each solution, children were instructed to drink as much as they wanted for 15 min. Then, the children rated the taste of the solution by marking a 100-mm

Table 1 | Summary of evidence published since 2008 on the management of acute gastroenteritis in children

	Intervention	Population	Main results (experimental group vs. control group)	Reference
ORS with improved taste	2 sucralose-sweetened ORSs vs. rice syrup solid ORS	N = 66 (5–10 years), healthy children	Sucralose-sweetened ORSs significantly more palatable (P < 0.001).	Freedman et al.[8]
	4 ORSs (cola, strawberry, fruit, neutral)	N = 116 (6–9 years), healthy children	Preference for cola (rated as good or really good by 87.9 %) and strawberry flavour (62.1 %).	Diez-Gandia et al.[9]
	Apple taste ORS vs. regular taste ORS	N = 130 (4–48 months) children with AGE	Similar resolution of signs of dehydration (P = 0.28), adequate weight gain (P = 0.48), urine production at 24 h (P = 0.95).	Pieścik-Lech et al.[10]
ORS with zinc	ORS with vs. ORS without zinc (40 mg/L)	N = 500 (boys, 1–35 months)	Similar stool output (P = 0.25); no difference or reduction in recovery time (HR 1.06, 95% CI 0.88 to 1.27).	Wadhwa et al.[11]
ORS with zinc and prebiotics	ORS with zinc (1 mmol/L) & prebiotics vs. standard ORS	N = 119 (3–36 months)	Higher resolution of diarrhoea at 72 h (P = 0.01); reduced number of daily outputs at 24 h (P = 0.002).	Passariello et al.[12]
ORS with polymers	Polymer-based ORS vs. glucose-based ORS	MA (34 RCTs, n = 4214)	Fewer unscheduled IV infusions (RR 0.75, 95% CI 0.59 to 0.95).	Gregorio et al.[13]
ORS with L-isoleucine	ORS with vs. ORS without L-isoleucine (2 g/L)	N=50 (boys, 6–36 months)	Reduced stool output on day 3 (P = 0.03); smaller ORS intake on day 1 (P = 0.04); similar duration of diarrhoea (P = 0.96).	Alam et al.[14]
ORS with honey	ORS with vs. ORS without honey	N = 100 (aged approx. 1.3 y)	Reduction in vomiting (P < 0.001) and diarrhoea frequency (P < 0.05).	Abdulrhman et al.[15]
Nasogastric rehydration	Rapid (4 h) vs. standard (24 h) nasogastric rehydration	N = 224 (6–72 months)	Similar primary treatment failure rates (>2 % weight loss during the study period) (P = 0.52).	Powell et al.[16]
Intravenous therapy	Ultrarapid (50 ml/kg/h) vs. standard (50 ml/kg/3h)	N = 88 (3–36 months)	Similar emesis volume, more urine volume, less stool output (P = 0.042).	Nager et al.[18]
Large vs. standard volume rehydration	Rapid (60 ml/kg) vs. standard (20 ml/kg) IV rehydration for 1 h	N = 223 children (3 months–11 years)	Similar proportions of rehydrated children at 2 h after initiation of treatment (P = 0.32).	Freedman et al.[19]

Table 1 | (Continued)

	Intervention	Population	Main results (experimental group vs. control group)	Reference
Antiemetics	Ondansetron (oral: 2–8 mg; 1.6–4 mg; IV: 0.15–0.3 mg/kg) vs. placebo.	MA (6 RCTs, $n = 745$, 1 month–12 years with vomiting and AGE)	Reduced risk of persistent vomiting (RR 0.45, 95% CI 0.33 to 0.62; NNT 5); reduced need for IV therapy (RR 0.41, 95% CI 0.28 to 0.62, NNT 5); and reduced risk of immediate hospital admission (RR 0.52, 95% CI 0.27 to 0.95, NNT 14). Increased diarrhoeal episodes (3 RCTs, data not pooled). No effect on return to care (RR 1.34, 95% CI 0.77 to 2.35).	DeCamp *et al.*[23]
	Ondansetron (oral: 2–8 mg; IV: 0.15–0.3 mg/kg) vs. placebo	MA (7 RCTs, $n = 760$, <18 y with vomiting and AGE)	Increased cessation of vomiting: (oral administration: 4 RCTs, RR 1.44, 95% CI 1.29 to 1.61; IV administration: 3 RCTs, RR 2.01, 95% CI 1.49 to 2.71; NNT 3). Reduced need for IV therapy: (oral administration, 4 RCTs, RR 0.41, 95% CI 0.29 to 0.59; NNT 5). Increased number of episodes of diarrhoea ($P < 0.05$).	Carter *et al.*[24]
Racecadotril	Racecadotril (typically 1.5 mg/kg TID) vs. placebo or equivalent (in particular, kaolin-pectin)	MA (9 RCTs, $n = 1384$, 1 months–15 years)	Higher proportion of patients with recovery defined as patients with a diarrhoea duration of less than 2 days (HR 2.04, 95% CI 1.85 to 2.32; $P < 0.001$). Reduced mean stool output in in-patients (HR 0.59, 95% CI 0.51 to 0.74; $P < 0.001$). Reduced mean number of diarrhoea stools in out-patients (HR 0.63, 95% CI 0.51 to 0.74; $P < 0.001$).	Lehert *et al.*[29]
Smectite	Smectite (6–12 g) vs. placebo.	$N = 602$ (1–36 months)	Peru: lower 72-h cumulative stool output ($P = 0.032$); shorter duration of diarrhoea ($P = 0.001$). Malaysia: lower 72-h stool output ($P = 0.007$); shorter duration of diarrhoea ($P = 0.001$).	Dupont *et al.*[30]
	Diosmectite (4.5 g/d for 5 days) vs. no intervention	$N=117$ (2–5 years) with AGE.	Shorter time for resolution of diarrhoea ($P < 0.001$).	Mujawr *et al.*[31]

Table 1 | (Continued)

	Intervention	Population	Main results (experimental group vs. control group)	Reference
Zinc	Zinc vs. placebo or zinc in other dose or no intervention	MA (18 RCTs, n = 11,180 with AGE, <5 years)	Reduced duration of diarrhoea (13 RCTs, n=5643, MD -0.7 day; 95% CI –0.97 to –0.40). Reduced the risk of diarrhoea lasting >7 days (8 RCTs, n = 5769, RR 0.71; 95% CI 0.53–0.96). Increased chance of vomiting (5 RCTs, n = 3156, RR 1.2; 95% CI 1.05-1.4).	Patro et al.[32]
	Zinc vs. placebo or no intervention	MA (26 RCTs, n = 20,480)	Shorter duration of diarrhoea (19 RCTs; n = 8957; shortened by 19.7 %; 95% CI 11.9 % to 27.4 %). Increased chance of vomiting (10 RCTs; n = 6779; OR 2.13; 95% CI 1.37–3.31). No effect on stool frequency and stool output.	Patel et al.[33]
	Zinc vs. placebo	MA (24 RCTs, n = 9128, age 1 month– 5 years)	Reduced duration of diarrhoea in children > 6 months (MD -10 h; 95% CI –21.12 to 0.25). Reduced duration of diarrhoea in malnourished children (MD –27 h; 95% CI –14.7 to –39).	Lazzerini et al.[34]
Probiotics (as a group)	Probiotics vs. placebo or no intervention.	MA (63 RCTs, n = 8014)	Reduced duration of diarrhoea (35 RCTs, n = 4555; MD –25 h; 95% CI 16 to 34); reduced risk of diarrhoea lasting ≥4 days (29 RCTs, n = 2853, RR 0.41, 95% CI 0.32 to 0.53).	Allen et al.[36]
Lactobacillus GG	Lactobacillus GG vs. placebo or no intervention	MA, 11 RCTs, n = 2072	Reduced duration of diarrhoea (MD –26.69; 95% CI –40.5 to –12.88, mean stool frequency on day 2 (6 RCTs, n = 1335; MD –0.76, 95% CI –1.32 to –0.2), and the risk of diarrhoea lasting ≥4 days (4 RCTs, n = 572; RR 0.59, 95% CI 0.40 to 0.87).	Allen et al.[36]
Saccharomyces boulardii	S. boulardii vs. placebo or no intervention	MA (10 RCTs, n = 860)	Reduced risk of diarrhoea lasting ≥4 days (6 RCTs, n = 606, RR 0.37; 95% CI 0.21 to 0.65; NNT 3, 95% CI 2–3).	Allen et al.[36]
	S. boulardii vs. placebo or no intervention	MA (9 RCTs, n = 1117)	Reduced duration of diarrhoea (MD 1.08 days, 95% CI 1.64-0.53).	Szajewska et al.[40]
	S. boulardii vs. placebo	N = 108 (3–59 months)	Reduced duration of diarrhoea (P = 0.03) Shorter time of appearance of first semi- formed stool (P = 0.008).	Riaz et al.[38]
	S. boulardii vs. placebo	N = 176 (6–48 months)	Reduced frequency of diarrhoea at day 2 (P < 0.01). Reduced frequency of diarrhoea at day 3 (P < 0.01).	Correa et al.[39]

Table 1 | (Continued)

	Intervention	Population	Main results (experimental group vs. control group)	Reference
L. reuteri ATCC 5573	*L. reuteri* ATCC 5573 vs. placebo	MA (2 RCTs, *n* = 106)	Reduced duration of diarrhoea (MD −25 h; 95% CI −39.4 to −10.9). Reduced risk of diarrhoea on day 1 (RR 0.88; 95% CI 0.8 to 0.99), on day 2 (RR 0.6; 95% CI 0.4 to 0.8), on day 3 (RR 0.45; 95% CI 0.3 to 0.8), and on day 4 (RR 0.36; 95% CI 0.1 to 0.7).	Chmielewska *et al.*[43]
L. reuteri DSM 17938	*L. reuteri* DSM 17938 vs. placebo	N = 74 (6–36 months)	Reduced duration of watery diarrhoea (*P* < 0.03). Smaller number of patients with persistent diarrhoea on day 2 (*P* < 0.01) and on day 3 (*P* < 0.03). Lower relapse rate (*P* < 0.03).	Francavilla *et al.*[45]
Synbiotics	5 probiotic strains & fructooligosaccharides vs. placebo	N = 111 (1–186 months)	Reduced duration of diarrhoea [3 days (IQR 2–4) vs. 4 days (IQR 4–5); *P* < 0.005].	Vandenplas *et al.*[51]
	L. paracasei B21060 plus arabinogalactan and xilooligosaccharides vs. placebo	N = 107 (3–36 months)	Higher rate of resolution of diarrhoea at 72 h (*P* = 0.005). Reduced duration of diarrhoea (*P* = 0.04). Reduced number of daily stool outputs from 48 to 72 h after treatment (*P* = 0.005).	Passariello *et al.*[52]

AGE, acute gastroenteritis; CI, confidence interval; HR, hazard ratio; IV, intravenous; MA, meta-analysis; OR, odds ratio; ORS, oral rehydration solution; RCT, randomised controlled trial; RR, risk ratio; MD, mean difference.

visual analogue scale (0 indicating the worst taste and 100, the best taste). Children consumed similar amounts of all 3 solutions. The sucralose-sweetened oral rehydration solutions were significantly more palatable than was the comparable rice-based solution. For convenience, this trial on taste was conducted in children who did not require oral rehydration. It is unclear whether similar findings would be found in children (especially in infants and young children) with AGE and dehydration. Similarly, another RCT documented variations in the acceptance of different flavours of ORS. However, again this study was carried out in healthy children aged 6–9 years.[9]

The efficacy and safety of a hypotonic ORS with an apple taste compared with a regular hypotonic ORS were recently assessed in 130 Polish children aged 4–48 months with AGE. The proportion of children with a resolution of signs of dehydration in the experimental group compared with the control group was similar at 24 h ($P = 0.28$). There were also no significant differences in adequate weight gain ($P = 0.48$) and urine production at 24 h ($P = 0.95$) between groups. There were no differences between groups in any of the secondary outcome measures, including ORS intake. Thus, this study showed that in an out-patient setting, both ORSs were equally effective and may be used interchangeably.[10]

ORS with zinc

One new RCT that involved 500 boys aged 1–35 months from India compared the use of ORS with zinc (40 mg/L) vs. use of ORS alone for the management of acute diarrhoea. There was no difference in the median stool output ($P = 0.25$) or in the time to recovery (HR: 1.06, 95% CI: 0.88–1.27) between groups. The results of this study are in contrast to earlier evidence from this region. However, the WHO-recommended daily dose of zinc for the management of diarrhoea was not achieved in most of the children beyond the first day of treatment.[11] Considering the study population and location, the results are not directly applicable to a high-income population.

ORS with zinc and prebiotics

One RCT performed in 119 Italian children aged 3–36 months with AGE and mild-to-moderate dehydration found a benefit of administering a hypotonic ORS containing zinc (1 mmol/L) and prebiotics (fructooligosaccharides and xilooligosaccharides – both 0.35 g/L). Compared with use of ORS alone, the use of ORS with zinc and prebiotics resulted in a higher rate of diarrhoea resolution at 72 h (50% vs. 72.9% respectively; $P = 0.01$), greater ORS intake during the first 24 h (50 mL/kg vs. 22 mL/kg respectively; $P < 0.001$), and a reduced number of missed working days by parents (0.39 vs. 1.45 days respectively; $P < 0.001$). While the results are promising, it is unclear which component – zinc, prebiotics, or both – was effective.[12]

ORS with polymers

It has been postulated that glucose polymer-based ORS (e.g. that prepared using rice or wheat) slowly releases glucose and may be superior to standard ORS. One new Cochrane review[13] (search date: September 2008) assessed the efficacy of using polymer-based ORS vs. glucose-based ORS for treating acute watery diarrhoea. Thirty-four RCTs ($n = 4214$) of variable methodological quality were available for analysis, among them 27 RCTs performed in children. Most compared polymer-based ORS with ORS with an osmolarity ≥ 310 mOsm/L. Compared with glucose-based ORS (ORS ≥ 310 mOsm/L and ≤ 270 mOsm/L groups combined), there were fewer unscheduled intravenous infusions in children in the polymer-based ORS group (19 RCTs, $n = 2235$, RR: 0.75, 95% CI: 0.59–0.95). Adverse effects were similar for those who received polymer-based ORS or glucose-based ORS. The authors' conclusion was that polymer-based ORS shows some advantages compared with glucose-based ORS (≥ 310 mOsm/L) for treating all-cause diarrhoea and diarrhoea caused by cholera. Limited evidence favoured the polymer-based ORS over the ORS ≤ 270 mOsm/L. Thus, for firm conclusions, further trials should compare the efficacy of the current standard ORS ≤ 270 mOsm/L with a polymer-based ORS.

ORS with L-isoleucine

On the basis of the hypothesis that L-isoleucine enhances the secretion of antimicrobial peptides in the intestinal epithelium, Alam et al.[14] evaluated the effects of L-isoleucine (2 g/L) added to standard ORS in a small RCT carried out in 50 boys with acute diarrhoea who live in Bangladesh. Compared with the standard ORS group, boys in the L-isoleucine-supplemented ORS group experienced some beneficial effects in terms of a reduction in stool output and ORS intake, although this was not consistent. No significant difference was observed in the duration of diarrhoea between the study groups (74 ± 38 h vs. 75 ± 42 h; $P = 0.96$). There was also no difference between groups in the concentration of antimicrobial peptides in the stools.

ORS with honey

Honey is considered to have anti-inflammatory and anti-microbial properties. Researchers in Egypt evaluated the effects of adding honey to ORS in an RCT that involved 100 infants and children with AGE. There was a significant reduction in vomiting ($P < 0.001$) and diarrhoea frequency ($P < 0.05$) in the honey-treated group compared with the control group (ORS alone). Also, the recovery time (i.e. time from the initiation of the intervention to the passage of the first normal stool, with normal hydration and satisfactory weight gain) was significantly shorter in the honey-treated group compared with the control group ($P < 0.001$).[15] Based on this single report, adding honey to ORS may be of benefit.

In summary, efforts to improve the taste and/or efficacy of ORS continue. While some interventions are promising, no major breakthrough has been made since the discovery of the scientific basis for oral rehydration and introduction of ORS into everyday practice. Furthermore, most studies were carried out in low-income countries, limiting their relevance to the Western world.

NASOGASTRIC REHYDRATION

According to current recommendations, when oral rehydration is not feasible, enteral rehydration by the nasogastric route is as effective as, if not better than, intravenous rehydration. In settings where nasogastric rehydration is common, the results of a recent study from Australia are of interest. Children aged 6–72 months with viral AGE and moderate dehydration were recruited ($n = 224$). Rapid (over 4 h) nasogastric rehydration was equally effective as a standard (24 h) nasogastric rehydration. The primary failure rates (>2% weight loss compared with the admission weight) were similar for the rapid rehydration group and the standard rehydration group (11.8% vs. 9.2% respectively; $P = 0.52$). There were no statistically significant differences between the study groups in persistent vomiting, dehydration scores, not tolerating the nasogastric tube, or parental concern. Secondary treatment failure was more common in the standard nasogastric rehydration group ($P = 0.03$). In general, rapid nasogastric rehydration reduced the need for hospitalisation; however, discharge from the emergency department failed in 27 of 132 (22.7%), and another 9 (7.6%) children were readmitted to the hospital within 24 h in this group.[16]

In summary, rapid nasogastric rehydration for 4 h was effective in children with AGE. As enteral rehydration, such as via nasogastric tube, is associated with significantly fewer major adverse events (e.g. electrolyte imbalances, cerebral oedema, phlebitis) than intravenous rehydration, the effectiveness of rapid nasogastric rehydration is of clinical relevance.

INTRAVENOUS REHYDRATION

Intravenous rehydration is the treatment of choice for severe dehydration and in cases of failure of oral rehydration therapy. However, the most appropriate method is still questionable. One of the discussions is focused on the volume and the rate of administration of fluid used for intravenous rehydration. Previously, it has been reported that evidence regarding rapid intravenous rehydration is lacking and can be correlated with side effects.[17]

Ultrarapid vs. rapid large-volume intravenous hydration

In the US, in a pilot trial carried out by Nager *et al.*,[18] 88 children aged 3–36 months with vomiting and/or diarrhoea and moderate dehydration who failed oral rehydration received either ultrarapid (50 mL/kg normal saline for 1 h) or rapid ('standard') intravenous rehydration (50 mL/kg normal saline for 3 h). Ultrarapid hydration for 1 h was comparable to standard 3-h hydration as assessed by the mean emesis volume (69 mL/h in the ultrarapid group vs. 63 mL/3 h in the standard group), urine volume (93 mL/h in the ultrarapid group vs. 71 mL/3 h in the standard group), and stool output (45 mL/h in the ultrarapid group vs. 75 mL/3 h in the standard group, $P = 0.042$). The two latter results should be considered with caution because of the differences in the hydrating time. There was no difference in the number of patients who needed to return to the Emergency Department between the groups (7 vs. 6 respectively; $P = 0.99$). No patient had complications, such as overhydration, seizures, deteriorating mental status, or laboratory abnormalities (although the study was underpowered for assessing harms). The authors concluded that the new hydrating regimen is an efficacious alternative, saves time, and allows earlier discharge of children from the emergency department.

Large-volume vs. standard-volume intravenous rehydration

The Canadian study by Freedman *et al.*[19] included 223 children aged 3 months–11 years with dehydration due to AGE, who had not responded to oral rehydration. Compared with standard intravenous rehydration (20 mL/kg), rapid intravenous rehydration (60 mL/kg), both with 0.9% saline over 1 h, resulted in similar

proportions of children with clinical rehydration 2 h after initiation of treatment (30% vs. 36% respectively, $P = 0.32$, NNT = 15). There were no differences between groups in any of the secondary outcomes, including prolonged treatment ($P = 0.18$), emergency department length of stay >6 h ($P = 0.78$), emergency department revisit resulting in admission ($P = 0.77$), and adequacy of oral intake. The median time to discharge was significantly longer in children rehydrated rapidly. Thus, this study documented that the current recommendation of administering 20 mL/kg per hour is adequate. Of note, the study methodology, especially the validity of the eight-point clinical dehydration scale, has been questioned by at least one author.[20]

Overall, new evidence regarding intravenous rehydration is not consistent. While there is no clear advantage of alternative approaches such as large-volume, rapid rehydration, future studies may contribute to resolving some uncertainties. In the absence of clear evidence, it is reasonable to follow the current recommendation of administering 20 mL/kg boluses.

EARLY VS. DELAYED RE-FEEDING

One Cochrane review[21] (search date: May 2011) compared the efficacy and safety of early (within 12 h of start of rehydration) and late (more than 12 h after start of rehydration) reintroduction of feeding in children younger than 10 years with acute diarrhoea. The search identified 12 RCTs ($n = 1283$) of variable methodological quality. Meta-analysis of the available data estimated no significant difference between the two groups in the number of participants who needed unscheduled intravenous fluids (6 RCTs, $n = 813$, RR 0.87, 95% CI: 0.48–1.59), who experienced episodes of vomiting (5 RCTs, $n = 456$, RR 1.16, 95% CI: 0.72–1.86), and who developed persistent diarrhoea (4 trials, $n = 522$, RR 0.57, 95% CI: 0.18–1.85). The mean length of hospital stay was also similar between groups (2 RCTs, $n = 246$). The authors of this meta-analysis stated that there was no evidence that early reintroduction of feeds increases the risk of unscheduled intravenous fluid use, episodes of vomiting and development of persistent diarrhoea. Also, no conclusion could be made regarding the duration of diarrhoea.

In summary, recent evidence does support the current recommendation for early reintroduction of regular feeding of children with AGE.

LACTOSE AVOIDANCE

The protocol of a systematic review on lactose avoidance for acute diarrhoea in children younger than 5 years has been published by The Cochrane Library.[22] However, at the time of writing this review, a full report was not available.

In summary, there is no basis to change the current ESPGHAN/ESPID guidelines stating that children with AGE can safely continue to consume lactose-containing milk formula.

ANTIEMETICS

Ondansetron

The authors of one meta-analysis (search date: 2008)[23] of 6 RCTs published subsequently to the ESPGHAN/ESPID guidelines found that ondansetron therapy (0.15–0.30 mg/kg for intravenous therapy or 2–8 mg orally) decreased the risk of persistent vomiting (5 RCTs, RR 0.45, 95% CI: 0.33–0.62; NNT 5), reduced the need for intravenous fluids (4 RCTs, RR 0.41, 95% CI: 0.28–0.62, NNT 5) and decreased the risk of immediate hospital admission (5 RCTs, RR 0.52, 95% CI: 0.27–0.95, NNT 14) in children with vomiting due to gastroenteritis. However, compared with placebo, ondansetron significantly increased diarrhoeal episodes in treated patients in 3 RCTs, and it did not have an effect on return to care (5 RCTs, RR 1.34, 95% CI: 0.77–2.35). The researchers concluded that future treatment guidelines should incorporate ondansetron therapy for selected children with gastroenteritis. They also suggested that given the costs related to intravenous therapy or hospitalisation, ondansetron therapy is likely to be cost-effective.

A more recent Cochrane Review (search date: March 2012)[24] included 7 RCTs that compared ondansetron (0.15–0.30 mg/kg intravenously or 2–8 mg orally) with placebo therapy and out of these, 4 RCTs investigated oral administration. Children younger than 18 years of age who presented with vomiting and had a clinical diagnosis of gastroenteritis were included. Compared with placebo, ondansetron significantly increased the proportion of children with cessation of vomiting (oral administration: 4 RCTs, $n = 574$, RR 1.44, 95% CI: 1.29–1.61, NNT 4, and intravenous administration: 3 RCTs, $n = 186$, RR 2.01, 95% CI: 1.49–2.71). The use of ondansetron also reduced the need for intravenous therapy (oral administration: RR 0.41, 95% CI: 0.29–0.59) and the immediate hospital admission rate (RR 0.40; 95% CI: 0.19–0.83). In 3 RCTs, there was an increased rate of episodes of diarrhoea in the ondansetron group ($P < 0.05$). The authors of the Cochrane review concluded that healthcare policy makers should consider the wider use of ondansetron.

On the basis of evidence available, only the Canadian Pediatric Society[25] recommended that oral ondansetron therapy, as a single dose, should be considered for children aged 6 months–12 years with vomiting related to suspected AGE, and who have mild-to-moderate dehydration or who have failed oral rehydration therapy. The use of ondansetron was not recommended in children with AGE manifested predominantly as moderate-to-severe diarrhoea, as one of the most common side effects of ondansetron is increased frequency of diarrhoea. Of note, although outside the context of diarrhoea, according to the FDA black box alert published in September 2011, electrocardiogram monitoring is recommended in patients receiving ondansetron with potential 'electrolyte abnormalities' due to the risk of developing prolongation of the QT interval, which can lead to an abnormal and potentially fatal heart rhythm, including Torsade de Pointes.[26]

Other antiemetics

Other antiemetic interventions studied using a meta-analytical approach have included administration of dexamethasone, dimenhydrinate, granisetron, and metoclopramide.[23, 24] From these, it can be concluded that there is no evidence to support the use of dexamethasone or metoclopramide, and there is only limited evidence that granisetron or dimenhydrinate stops vomiting. With regard to the latter, one more trial published after the Cochrane review was identified. This double-blind RCT confirmed that compared with placebo, oral dimenhydrinate had no effect on the frequency of vomiting in children 1–12 years of age with AGE.[27]

The protocol for a new multicentre RCT comparing oral ondansetron vs. domperidone for symptomatic treatment of vomiting during acute gastroenteritis in children has been published that will shed light on the remaining uncertainties.[28]

In summary, new evidence indicates that ondansetron, at the dosages used in the studies and administered orally or intravenously, may be considered for use in young children with vomiting related to AGE. However, before a final recommendation is made, a clearance on safety in children is needed. There is no evidence to support the use of other antiemetics.

RACECADOTRIL

A recent individual patient data meta-analysis[29] (search date: December 2010) assessed the efficacy of the use of racecadotril as an adjunct to ORS compared with ORS alone or with placebo. Raw data from 9 RCTs involving 1348 children aged 1 month to 15 years with AGE were available for the analysis. The experimental treatment was compared with placebo, with no treatment (2 RCTs), or with kaolin-pectin (2 RCTs; the latter was not in line with the authors' objectives). There were 4 studies in the in-patient setting, and 5 studies in the out-patient setting. Compared with placebo, racecadotril significantly reduced the duration of diarrhoea after inclusion (2.81 vs. 1.75 days respectively). Almost two times more patients recovered at any time in the racecadotril group vs. the placebo group (HR 2.04, 95% CI: 1.85–2.32; $P < 0.001$). There were no interactions between treatment and dehydration, rotavirus infection, type of study (out-patient/in-patient), or country. In the studies evaluating in-patients, the ratio of mean stool output racecadotril/placebo was reduced (0.59, 95% CI: 0.51–0.74; $P < 0.001$). In out-patient studies, the number of diarrhoeal stools was lower in the racecadotril group (mean ratio racecadotril/placebo: 0.63, 95% CI: 0.51–0.74, as *per abstract*; $P < 0.001$). In the responder analysis (defined as a duration of diarrhoea of less than 2 days), the proportion of responders was significantly higher in the racecadotril group compared with the placebo group (50.3% vs. 25.8% respectively). By adjusting for dehydration and rotavirus, the absolute risk difference was 24.7% (95% CI: 19.8–29.7), and the associated number needed to treat was 4. The secondary need for care in out-patients was significantly in favour of racecadotril in 2 studies. Also, the need for intravenous therapy was lower in the racecadotril group compared with the placebo group. There was no difference in the incidence of adverse events between the groups.

In summary, the results of a recent meta-analysis based on individual patient data do support the use of racecadotril, as an adjunct to ORS, for the management of AGE in children.

DIOSMECTITE

Two new RCTs were published. However, neither of them was performed in a high-income country. Dupont *et al.*[30] performed 2 parallel, double-blind studies of diosmectite efficacy on stool reduction in 602 children (age range: 1–36 months) with acute watery diarrhoea from 2 countries (Peru and Malaysia). Children who needed intravenous therapy, had gross blood in their stools, had a fever >39°C, or were undergoing current treatment with antidiarrhoeal or antibiotic medications were excluded. Children randomly received diosmectite (6 g/day for children 1–12 months of age or 12 g/day for children 13–36 months of age; given for at least

3 days, followed by half doses until complete recovery) or placebo in addition to ORS. The results are presented separately for the two populations, because of the differences in the definitions of some of the outcomes. In Peru ($n = 300$), in the diosmectite group compared with the placebo group, there was reduced 72-h cumulative stool output (102.0 ± 65.5 g/kg vs. 118.8 ± 92.5 g/kg respectively; $P = 0.032$) and a shorter duration of diarrhoea (median, 68.17 h vs. 118.92 h respectively; $P = 0.001$). The positive effect of diosmectite was confirmed in both rotavirus-positive and rotavirus-negative children. In Malaysia ($n = 302$), the 72-h stool output was also significantly less in children who received diosmectite than in controls (87.9 ± 81.2 g/kg vs. 90.7 ± 94.0 g/kg respectively; $P = 0.007$). The median duration of diarrhoea was significantly shorter in children who received diosmectite than in controls (median, 25.1 h vs. 32.6 h respectively; $P = 0.001$); however, the beneficial effect was observed in rotavirus-negative children only.

The more recent open RCT carried out in India also found that diosmectite reduced the duration of diarrhoea and prevented a prolonged course.[31] In this study, 117 children aged 2–5 years with watery diarrhoea for <48 h and mild-to-moderate dehydration were randomised to receive ORS and diosmectite (1.5 g, three times a day, for 5 days) or ORS only. In the diosmectite group compared with the control group, the time for resolution of the diarrhoea was significantly shorter (64.34 ± 14.86 h vs. 82.37 ± 21.43 h respectively; $P < 0.001$) as was the total duration of diarrhoea (91.45 ± 17.53 h vs. 107.53 ± 25.68 h respectively; $P < 0.001$).

In summary, although both recent studies were carried out outside Europe, the findings reconfirmed that diosmectite, as an adjuvant to standard rehydration therapy, may provide benefit in the management of children with AGE.

ZINC

To our knowledge, there have now been at least 3 new meta-analyses on the use of zinc for treating AGE in children. The first one (search date: November 2007; published in 2008) identified 18 RCTs (11,180 participants). Use of zinc (15–40 mg/day depending on age) was associated with a significant reduction in diarrhoea duration and the risk of diarrhoea lasting longer than 7 days, but no significant reduction in stool volumes. The authors concluded that zinc supplementation can be useful for treating AGE in children. However, most of the studies were performed in developing countries where zinc deficiency is common.[32]

The second meta-analysis (search date: not stated) found that zinc supplementation reduced the mean duration of acute diarrhoea by 19.7% (19 RCTs, $n = 8,957$) and the mean duration of persistent diarrhoea by 15–30%; however, zinc supplementation had no effect on stool frequency or stool output, and it increased the risk of vomiting.[33]

The most recent review[34] (search date: February 2012) identified 19 RCTs comparing oral zinc supplementation (10–40 mg/day depending on age) with placebo in children aged 1 month–5 years with acute diarrhoea, who were mainly from developing countries where zinc deficiency is common. Interestingly, in children younger than 6 months, zinc supplementation had no effect on the mean duration of diarrhoea (2 RCTs, $n = 1334$, low-quality evidence, MD – 5.23 h, 95% CI: –4 to 14.45), and it may increase the risk of diarrhoea persisting until day 7 (1 RCT, $n = 1074$, moderate-quality evidence, RR 1.24, 95% CI: 0.99–1.54). In children older than 6 months, the administration of zinc reduced the duration of diarrhoea (5 RCTs, $n = 2091$, low-quality evidence, MD – 10.44 h, 95% CI: –21.13 to 0.25), and it reduced the risk of diarrhoea persisting until day 7 (6 RCTs, $n = 3865$, moderate-quality evidence, RR 0.73, 95% CI: 0.61–0.88).

For the European population, there was only one RCT carried out in 141 Polish children with AGE aged 3–48 months. These children were randomised to receive zinc sulphate (10 or 20 mg/day depending on age) or placebo for 10 days. There was no significant difference in the duration of diarrhoea between groups ($P>0.05$). Similarly, there was no significant difference between the groups in secondary outcome measures, such as stool frequency on days 1, 2, and 3, vomiting frequency, intravenous fluid intake, and the number of children with diarrhoea lasting >7 days.[35]

At least one large trial in a high-income country (US) on oral zinc for the treatment of acute diarrhoea is currently in progress (clinicaltrials.gov NCT01198587).

In summary, recent data provide further evidence that children older than 6 months living in developing countries may benefit from the use of zinc in the treatment of AGE. However, in regions where zinc deficiency is rare, no benefit from the use of zinc was documented.

PROBIOTICS

In an update to a previously published Cochrane review, Allen et al.[36] pooled data from 63 RCTs ($N = 8014$) that evaluated the efficacy of probiotics for the treatment of acute infectious diarrhoea in subjects of all ages.

Probiotics (as a group) reduced the duration of diarrhoea (35 RCTs, *n* = 4555; MD -25 h; 95% CI: 16–34) and the risk of diarrhoea lasting ≥ 4 days (29 RCTs, *n* = 2853, RR 0.41, 95% CI: 0.32–0.53).

The majority of the trials (56 RCTs) were carried out in infants and young children. Forty-six RCTs tested a single probiotic, and 17 RCTs tested a combination of 2 to 8 probiotics. The 2 most commonly studied probiotics were *Lactobacillus* GG (13 RCTs) and *S. boulardii* (10 RCTs). The remaining probiotics or their combinations were evaluated in 5 or fewer studies. As pooling data on different probiotics has been repeatedly questioned, evidence on each probiotic strain (or their combinations) should be evaluated separately.[37]

Lactobacillus rhamnosus GG

LGG is considered particularly effective in the management of AGE. This was confirmed by the updated Cochrane review documenting that LGG reduced the duration of diarrhoea (11 RCTs, *n* = 2072; MD: −26.69; 95% CI: −40.5 to −12.88), mean stool frequency on day 2 (6 RCTs, *n* = 1335; MD: −0.76, 95% CI: −1.32 to −0.2), and the risk of diarrhoea lasting ≥ 4 days (4 RCTs, *n* = 572; RR: 0.59, 95% CI: 0.40–0.87).[36]

Saccharomyces boulardii

At least 2 new RCTs[38, 39] and 3 systematic reviews have confirmed the beneficial effects of *S. boulardii*. The updated meta-analysis[40] (search date: August 2009) of 9 RCTs (*n* = 1117), compared with 5 RCTs (*n* = 619) included in the original meta-analysis,[41] confirmed that in otherwise healthy infants and children, the use of *S. boulardii* reduces the duration of diarrhoea by approximately 1 day. In addition, a Cochrane review (search date: July 2010) documented that *S. boulardii* reduced the risk of diarrhoea lasting ≥ 4 days (6 RCTs, *n* = 606, RR: 0.37; 95% CI: 0.21–0.65; NNT 3, 95% CI: 2–3).[36] Finally, the authors of the most recent review (search date: October 2011) confirmed that use of *S. boulardii* significantly reduced the duration of diarrhoea (approximately 24 h) and hospitalisation (20 h). The authors' conclusion was that both effects result in social and economic benefits.[42]

Lactobacillus reuteri

Previously, the pooled results from 2 RCTs (*n* = 106) documented that *L. reuteri* ATCC 55730 reduced the duration of diarrhoea as well as the risk of diarrhoea on days 1, 2 and 3 of an illness.[43] As the *L. reuteri* ATCC 55730 strain was found to carry potentially transferable resistance traits for tetracycline and lincomycin, it was replaced by a new strain, *L. reuteri* DSM 17938, with no unwanted plasmid-borne resistances.[44] Recently, one RCT evaluated the efficacy of treatment with *L. reuteri* DSM 17938 (dose of 4 × 10^8 CFU) compared with placebo in 74 Italian children aged 6–36 months hospitalised for acute diarrhoea. Administration of *L. reuteri* DSM 17938 compared with placebo significantly reduced the duration of watery diarrhoea (2.1 ± 1.7 vs. 3.3 ± 2.1 days respectively; *P* < 0.03), the risk of diarrhoea on day 2 (55% vs. 82% respectively; *P* < 0.01) and on day 3 (45% vs. 74% respectively; *P* < 0.03), and the relapse rate of diarrhoea (15% vs. 42% respectively; *P* < 0.03). The duration of hospital stay was similar in both groups.[45]

Other probiotics

A number of studies on various probiotics (single or in combinations) were published subsequently to the ESPGHAN/ESPID guidelines.[46–49] Many reported a shortened duration of diarrhoea in the probiotic(s)-treated group.

In summary, new evidence has confirmed that the probiotics currently supported by ESPGHAN/ESPID – *Lactobacillus* GG and *S. boulardii* – are effective in reducing the duration of diarrhoea. Current evidence clearly indicates that these are not the only effective probiotic microorganisms; however, these are the most studied. Probiotic effects are strain-specific, so the efficacy and safety of each should be established. The safety and clinical effects of 1 probiotic microorganism should not be extrapolated to other probiotic microorganisms. The role of probiotics in the treatment of AGE in the era of rotavirus vaccination has yet to be established.

SYNBIOTICS

Synbiotics are defined as a combination of prebiotics and probiotics that beneficially affect the host by improving survival and implantation of live microbial dietary supplements in the gastrointestinal tract.[50] Previously, synbiotics were not addressed in the ESPGHAN/ESPID guidelines due to a lack of data. Two recent RCTs evaluated the efficacy of synbiotics for the management of AGE. In the first RCT,[51] researchers from Belgium compared the efficacy of 5 probiotic strains *(Str. thermophilus, L. rhamnosus, L. acidophilus, B. lactis, B. infantis)* and fructooligosaccharides in 111 children with acute diarrhoea (median age: 40 months). Compared with the placebo group, the median duration of diarrhoea was significantly shorter in the synbiotic group [3 days (IQR: 2–4) vs. 4 days (IQR: 4–5); *P* < 0.005]. In the synbiotic

Table 2 | Summary of new evidence on the management of acute gastroenteritis in children

Oral rehydration	Remains central to the management of children with AGE. Efforts to improve the taste and/or efficacy of ORS continue, and some interventions are promising.
Nasogastric rehydration	While standard (over 24 h) nasogastric rehydration is still being used, new evidence confirms that rapid (over 4 h) nasogastric rehydration is also effective.
Intravenous rehydration	New evidence is available regarding rapid or ultrarapid and large-volume vs. standard-volume rehydration. As the new evidence is not consistent, until more data are available, the administration of 20 ml/kg is appropriate.
Antiemetics	Ondansetron reduces the risk of vomiting in young children with AGE, but there is no evidence to support the use of other antiemetics. The FDA recommends electrocardiogram monitoring of the QT interval in patients receiving ondansetron.
Zinc	Evidence from one study in Europe, where zinc deficiency is rare, confirms no benefit from the use of zinc.
Racecadotril	Data, mainly from outside of Europe, have reconfirmed that racecadotril may be an effective adjunctive therapy to oral rehydration.
Smectite	Data, mainly from outside of Europe, have reconfirmed that smectite may be an effective adjunctive therapy to oral rehydration.
Probiotics	Certain probiotics, such as *Lactobacillus* GG or *S. boulardii,* are useful. It is likely that many more probiotics are effective; the current lack of clear evidence of efficacy does not mean that future clinical research will not establish significant health benefits for other probiotics (single or in combination). The same applies to synbiotics.

group compared with the placebo group, the number of children with normalised stool consistency was higher at day 2 (21% vs. 2% respectively; $P < 0.001$) and at day 3 (50% vs. 24%, $P < 0.001$). Moreover, in the synbiotic group, less additional medications (antipyretics, antiemetics, antibiotics) were administered.

In the second RCT,[52] researchers in Italy demonstrated that another synbiotic combination (*L. paracasei* B21060 plus arabinogalactan and xilooligosaccharides) also appears to offer benefit. In this study that involved 107 children aged 3–36 months with acute diarrhoea, the rate of resolution of diarrhoea at 72 h was significantly higher in children who received the synbiotic combination compared with placebo (67% vs. 40% respectively; $P = 0.005$). Moreover, compared with the placebo group, children in the synbiotic group experienced a statistically significant reduction in the total duration of diarrhoea (109.8 h vs. 90.5 h respectively; $P = 0.04$), number of stool outputs from 48 to 72 h after treatment (3.3 vs. 2.4 respectively; $P = 0.005$), and stool consistency score from 48 to 72 h after treatment (1.3 vs. 0.6 respectively; $P = 0.002$). The percentage of patients requiring hospitalisation, the percentage of parents who missed at least one working day and the rate of use of adjunct medications were also significantly lower in the synbiotic group compared with the placebo group.

In summary, the studies on synbiotics are promising. However, it would not be appropriate to recommend use of any of the synbiotics studied thus far until confirmatory data are available.

CONCLUSIONS

This review summarised the most recent data on the management of AGE published subsequently (i.e. after 2008) to the ESPGHAN/ESPID guidelines (Table 2). The update of current recommendations is warranted.

REFERENCES

1. Guarino A, Albano F, Ashkenazi S, *et al.*; Expert Working Group. The ESPGHAN/ESPID evidenced-based guidelines for the management of acute gastroenteritis in children in Europe. *J Pediatr Gastroenterol Nutr* 2008; **46** (Suppl. 2): S81–122.

2. Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health* 1990; **2012**: 220.

3. Black RE, Cousens S, Johnson HL, *et al.* Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010; **375**: 1969–87.

4. Lo Vecchio A, Giannattasio A, Duggan C, *et al.* Evaluation of the quality of guidelines for acute gastroenteritis in children with the AGREE instrument. *J Pediatr Gastroenterol Nutr* 2011; **52**: 183–9.

5. National Institute for Health and Clinical Excellence. Diarrhoea and vomiting in children. Diarrhoea and vomiting caused by gastroenteritis: diagnosis, assessment and management in children younger than 5 years. April 2009. Available at: http://www.nice.org.uk/nicemedia/live/11846/47350/47350.pdf.

6. Guarino A, Albano F, Guandalini S; For the ESPGHAN Working Group on Acute Diarrhea. Oral rehydration solution: toward a real solution. *J Pediatr Gastroenterol Nutr* 2001; **33** (Suppl. 2): S2–12.

7. Szajewska H, Hoekstra JH, Sandhu B. Management of acute gastroenteritis in Europe and the impact of the new recommendations: a multicenter study. *J Pediatr Gastroenterol Nutr* 2000; **30**: 522–7.

8. Freedman SB, Cho D, Boutis K, Stephens D, Schuh S. Assessing the palatability of oral rehydration solutions in school-aged children: a randomized crossover trial. *Arch Pediatr Adolesc Med* 2010; **164**: 696–702.

9. Diez-Gandia A, Ajenjo MA, Navalón AB, Fernández RB, Sanz AB, Dőez-Domingo J. Palatability of oral rehydration solutions (ORS) in healthy 6 to 9 year-old children. A multicentre, randomised single blind clinical trial. *An Pediatr (Barc)* 2010; **72**: 111–5.

10. Pieścik-Lech M, Szymański H, Szajewska H. Efficacy and safety of a new apple flavoured oral rehydration solution in children with acute gastroenteritis: a doubleblind randomized controlled trial. *Acta Paediatr* 2012; **101**: e458–64.

11. Wadhwa N, Natchu UC, Sommerfelt H, *et al.* ORS containing zinc does not reduce duration or stool volume of acute diarrhea in hospitalized children. *J Pediatr Gastroenterol Nutr* 2011; **53**: 161–7.

12. Passariello A, Terrin G, De Marco G, *et al.* Efficacy of a new hypotonic oral rehydration solution containing zinc and prebiotics in the treatment of childhood acute diarrhea: a randomized controlled trial. *J Pediatr* 2011; **158**: e1.

13. Gregorio GV, Gonzales ML, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database Syst Rev* 2009; **15**: CD006519.

14. Alam NH, Raqib R, Ashraf H, *et al.* L-isoleucine-supplemented oral rehydration solution in the treatment of acute diarrhoea in children: a randomized controlled trial. *J Health Popul Nutr* 2011; **29**: 183–90.

15. Abdulrhman MA, Mekawy MA, Awadalla MM, Mohamed AH. Bee honey added to the oral rehydration solution in treatment of gastroenteritis in infants and children. *J Med Food* 2010; **13**: 605–9.

16. Powell CV, Priestley SJ, Young S, Heine RG. Randomized clinical trial of rapid versus 24-hour rehydration for children with acute gastroenteritis. *Pediatrics* 2011; **128**: e771–8.

17. Gorelick MH. *Rapid Intravenous Rehydration in the Emergency Department: A Systematic Review.* Pediatric Emergency Medicine Database 2002. Available at: http://www.pemdatabase.org/files/rapid_iv_hydration_23.07.doc. Accessed September 15, 2012.

18. Nager AL, Wang VJ. Comparison of ultrarapid and rapid intravenous hydration in pediatric patients with dehydration. *Am J Emerg Med* 2010; **28**: 123–9.

19. Freedman SB, Parkin PC, Willan AR, Schuh S. Rapid versus standard intravenous rehydration in paediatric gastroenteritis: pragmatic blinded randomised clinical trial. *BMJ* 2011; **343**: d6976.

20. Nager AL. Intravenous rehydration in paediatric gastroenteritis. *BMJ* 2011; **343**: d7083.

21. Gregorio GV, Dans LF, Silvestre MA. Early versus delayed refeeding for children with acute diarrhoea. *Cochrane Database Syst Rev* 2011; **7**: CD007296.

22. MacGillivray S, Fahey T, McGuire W. Lactose avoidance for acute diarrhoea in children less than five years. *Cochrane Database Syst Rev* 2005; **3**: CD005433.

23. DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med* 2008; **162**: 858–65.

24. Carter B, Fedorowicz Z. Antiemetic treatment for acute gastroenteritis in children: an updated Cochrane systematic review with meta-analysis and mixed treatment comparison in a Bayesian framework. *BMJ Open* 2012; **2**.

25. Cheng A. Emergency department use of oral ondansetron for acute gastroenteritisrelated vomiting in infants and children. *Paediatr Child Health* 2011; **16**: 177–82.

26. Food and Drug Administration. The FDA Safety Information and Adverse Event Reporting Program. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm272041.htm.

27. Gouin S, Vo TT, Roy M, *et al.* Oral dimenhydrinate versus placebo in children with gastroenteritis: a randomized controlled trial. *Pediatrics* 2012; **129**: 1050–5.

28. Marchetti F, Maestro A, Rovere F, *et al.* Oral ondansetron versus domperidone for symptomatic treatment of vomiting during acute gastroenteritis in children: multicenter randomized controlled trial. *BMC Pediatr* 2011; **11**: 15.

29. Lehert P, Chéron G, Calatayud GA, *et al.* Racecadotril for childhood gastroenteritis: an individual patient data meta-analysis. *Dig Liver Dis* 2011; **43**: 707–13.

30. Dupont C, Foo JL, Garnier P, *et al.* Oral diosmectite reduces stool output and diarrhea duration in children with acute watery diarrhea. *Clin Gastroenterol Hepatol* 2009; **7**: 456–62.

31. Mujawr QM, Naganoor R, Ali MD, *et al.* Efficacy of dioctahedral smectite in acute watery diarrhea in Indian children: a randomized clinical trial. *J Trop Pediatr* 2012; **58**: 63–7.

32. Patro B, Golicki D, Szajewska H. Meta-analysis: zinc supplementation for acute gastroenteritis in children. *Aliment Pharmacol Ther* 2008; **28**: 713–23.

33. Patel A, Mamtani M, Dibley MJ, Badhoniya N, Kulkarni H. Therapeutic value of zinc supplementation in acute and persistent diarrhea: a systematic review. *PLoS ONE* 2010; **5**: e10386.

34. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. *Cochrane Database Syst Rev* 2012; **6**: CD005436.

35. Patro B, Szymański H, Szajewska H. Oral zinc for the treatment of acute gastroenteritis in Polish children: a randomized, double-blind, placebo-controlled trial. *J Pediatr* 2010; **157**: e1.

36. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev* 2010; **11**: CD003048.

37. Szajewska H. Advances and limitations of evidence-based medicine – impact for probiotics. *Ann Nutr Metab* 2010; **57**(Suppl.): 6–9.

38. Riaz M, Alam S, Malik A, Ali SM. Efficacy and safety of Saccharomyces boulardii in acute childhood diarrhea: a double blind randomised controlled trial. *Indian J Pediatr* 2012; **79**: 478–82.

39. Corrêa NB, Penna FJ, Lima FM, Nicoli JR, Filho LA. Treatment of acute diarrhea with Saccharomyces boulardii in infants. *J Pediatr Gastroenterol Nutr* 2011; **53**: 497–501.

40. Szajewska H, Skórka A. Saccharomyces boulardii for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials. *Aliment Pharmacol Ther* 2009; **30**: 955–63.

41. Szajewska H, Skorka A, Dylag M. Meta-analysis: Saccharomyces boulardii for treating acute diarrhoea in children. *Aliment Pharmacol Ther* 2007; **25**: 257–64.

42. Dinleyici EC, Eren M, Ozen M, et al. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. *Expert Opin Biol Ther* 2012; **12**: 395–410.

43. Chmielewska A, Ruszczyński M, Szajewska H. Lactobacillus reuteri strain ATCC 55730 for the treatment of acute infectious diarrhoea in children: a meta-analysis of randomized controlled trials. *Pediatria Współczesna. Gastroenterologia, Hepatologia i Żywienie Dziecka* 2008; **10**: 33–7.

44. Rosander A, Connolly E, Roos S. Removal of antibiotic resistance plasmids from *Lactobacillus reuteri* ATCC 55 730 and characterization of the resulting daughter strain, L reuteri DSM 17 938. *Appl Environ Microbiol* 2008; **74**: 6032–40.

45. Francavilla R, Lionetti E, Castellaneta S, et al. Randomised clinical trial: Lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea - a double-blind study. *Aliment Pharmacol Ther* 2012; **36**: 363–9.

46. Chen CC, Kong MS, Lai MW, et al. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhea. *Pediatr Infect Dis J* 2010; **29**: 135–8.

47. Grandy G, Medina M, Soria R, Terán CG, Araya M. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. *BMC Infect Dis* 2010; **10**: 253.

48. Rerksuppaphol S, Rerksuppaphol L. *Lactobacillus acidophilus* and *Bifidobacterium bifidum* stored at ambient temperature are effective in the treatment of acute diarrhoea. *Ann Trop Paediatr* 2010; **30**: 299–304.

49. Dutta P, Mitra U, Dutta S, et al. Randomised controlled clinical trial of *Lactobacillus sporogenes* (*Bacillus coagulans*), used as probiotic in clinical practice, on acute watery diarrhoea in children. *Trop Med Int Health* 2011; **16**: 555–61.

50. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics–approaching a definition. *Am J Clin Nutr* 2001; **73**(Suppl.): 361S–4S.

51. Vandenplas Y; PROBIOTICAL-study group. Randomised clinical trial: the synbiotic food supplement Probiotical vs. placebo for acute gastroenteritis in children. *Aliment Pharmacol Ther* 2011; **34**: 862–7.

52. Passariello A, Terrin G, Cecere G, et al. Randomised clinical trial: efficacy of a new synbiotic formulation containing *Lactobacillus paracasei* B21060 plus arabinogalactan and xilooligosaccharides in children with acute diarrhoea. *Aliment Pharmacol Ther* 2012; **35**: 782–8.