

## Overview of Reviews

# Treatment of acute gastroenteritis in children: an overview of systematic reviews of interventions commonly used in developed countries

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**Background:** Acute gastroenteritis (AGE) is an extremely common paediatric condition, which results in significant morbidity in children and is a financial burden to the society.

**Objective:** The purpose of this overview is to critically evaluate the evidence currently available in the *Cochrane Database of Systematic Reviews* (CDSR) regarding the efficacy and safety of commonly considered treatment options in children with AGE.

**Methods:** All Cochrane reviews evaluating the following treatments in children with AGE were eligible for inclusion: oral rehydration therapy, anti-emetics and probiotics. We excluded those focusing on the treatment of antibiotic associated or nosocomial diarrhoea, persistent (chronic) diarrhoea and the prevention of gastroenteritis. We focused on the following outcomes that were selected a priori as clinically important: rate of admission to the hospital; length of stay in hospital; rate of return visits; administration of intravenous (IV) therapy owing to failure of oral rehydration therapy; adverse events and dysnatremia.

**Main results:** Children who received oral rehydration therapy had a shorter length of stay in hospital compared with children who received IV therapy [mean difference, MD = -1.20 days (-2.38, -0.02)]; however, the result was no longer significant when an outlying study was removed. Children who received IV therapy were at increased risk of developing phlebitis [risk difference, RD = -0.02 (-0.04, -0.01)], while paralytic ileus was more common in children receiving ORT [RD = 0.03 (confidence interval, CI 0.01–0.05)]. Children who received oral ondansetron had lower hospital admission rates to the emergency department (ED) and lower rates of IV rehydration during their ED stay compared with children receiving placebo [risk ratio, RR = 0.40 (CI 0.19–0.83) and RR = 0.41 (CI 0.29–0.59), respectively]. Children receiving IV ondansetron had lower hospital admission rates to the ED than patients receiving placebo [RR = 0.21 (0.05, 0.93)]. Probiotic use amongst children hospitalized following AGE reduced the mean duration of hospitalization by 1.12 days (CI -1.16, -0.38).

**Conclusions:** Given that oral rehydration is less invasive than IV rehydration with no evidence of important clinical differences, it is the first choice for rehydration in children with AGE and mild-to-moderate dehydration. As the vast majority of children with AGE do not require IV rehydration, oral ondansetron administration to children with significant vomiting should be performed to reduce the use of IV rehydration and the need for hospital admission. In children deemed too unwell to receive oral rehydration therapy, IV ondansetron administration is an option, as its use is associated with lower hospital admission rates. Although probiotics appear to be an effective option for the treatment of AGE amongst hospitalized children, outpatient data is lacking and more studies are urgently needed to determine the optimal organism, dosing and duration of treatment.

**Keywords:** anti-emetics, dehydration, diarrhoea, gastroenteritis, probiotics, rehydration, vomiting

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## Plain language summary

Acute gastroenteritis (AGE) is characterized by fever, vomiting and diarrhoea. Although it is a common disease in children and adolescents, debate continues regarding the routine use of many potential treatment options. In this overview, we focus on the use of rehydration therapy, anti-vomiting drugs (anti-emetics) and probiotics; although other interventions may be relevant in developing countries, we chose to focus on those most often considered for use in developed countries. As there are no important clinical differences between children treated with oral rehydration therapy and those administered intravenous (IV) rehydration therapy, oral therapy should be the initial approach used in children with mild-to-moderate dehydration. Children who received the anti-emetic agent ondansetron orally were less likely to be administered IV rehydration compared with those given placebo. In addition, both oral and IV ondansetron administration are associated with reductions in the need for hospitalization when used in the emergency department. The evidence reveals that probiotics reduce time spent in hospital by over a day. Although probiotics appear to be effective, more research to determine the optimal therapeutic regimen is needed. In addition, although limited, the available data currently does not support the routine use of probiotics in outpatients.

## Background

### Description of the condition

Acute gastroenteritis (AGE) is an extremely common disease characterized by diarrhoea, vomiting and fever. The diagnosis of AGE is a clinical one based on a child's clinical presentation. The occurrence of at least three loose or watery stools (taking the shape of the container) in a 24-hour period is generally required to confirm the presence of diarrhoea. Since the aetiological agents in developed countries are most commonly viruses (1), treatment remains primarily supportive.

Although rarely resulting in death in developed countries, globally, diarrhoeal disease is responsible for approximately 10% of deaths in children under 5 years of age (2). In absolute numbers, this represents over 800 000 deaths each year (2). In developed countries such as Canada however, AGE continues to exert a significant burden, accounting for nearly 240 000 emergency department (ED) visits annually (3), and the hospitalization of one in 25 children by 5 years of age (4). In 2001, the annual cost per 100 000 population in Canada was \$11 465 541 (5). The burden is similarly significant amongst children under 5 years of age in the US where the estimated overall incidence is two episodes of diarrhoeal illness annually, and direct costs for hospital and outpatient care are estimated to exceed \$2 billion per year (6).

### Description of the intervention

Despite being a ubiquitous illness, there exists significant worldwide variation in the management of gastroenteritis. In North America, variation exists at institutional (7), national (8) and international (Canada/US) levels (9). Recently, a paediatric emergency medicine (PEM) physicians practice pattern survey (9) and prospective cross-Canada practice pattern analysis (8) documented substantial variation across North America and within Canadian academic paediatric EDs. Such variation may stem from inconsistent implementation of clinical practice guidelines (CPG) or medical directives, as evidenced by a recently conducted survey demonstrating that only 28% of Ontario EDs have a gastroenteritis CPG/pathway and only 38% have an oral rehydration therapy medical directive (10). Lack of such clinical guidance may be due, in part, to a need for cohesive summaries regarding treatment options and their effectiveness.

### How the interventions might work

Clinicians providing care to children with gastroenteritis have to make several key treatment decisions. Likely the most crucial and most common relates to the choice of which rehydration method to employ (i.e. oral versus IV). Position statements by the Canadian Pediatric Society (CPS) (11), the American Academy of Pediatrics (AAP) (12), as well as a Cochrane Review (13) endorse the use of oral rehydration therapy (ORT) in all children with evidence of mild-to-moderate dehydration and also to prevent dehydration amongst euvolemic children. Nonetheless, there continues to be variation in clinical practice with a self-reported 29% absolute difference in its routine usage between the US and Canadian PEM physicians (9). Consequently, research regarding its use continues to emerge; reviewing and updating the current evidence may provide a more solid evidence base for informed and consistent practice.

The use of anti-emetics is highly controversial, variable and a topic of great importance. Although popular in Canada, dimenhydrinate is rarely used elsewhere (14) and has been the topic of two recent clinical trials (15, 16). Ondansetron use is debated as well; a recent systematic review concluded that the evidence favouring ondansetron use is limited (17), while an earlier systematic review (18) and a recent CPS position statement (19) concluded that the use of ondansetron results in clinical benefits and it should be incorporated into guidelines. In response to a recent AAP guideline statement that 'cost-effectiveness analyses [for ondansetron] should be undertaken' (20), an analysis was recently performed and demonstrated that appropriate use would result in an annual savings of \$1.7 million to Canadians and \$66 million to Americans (3). The varying conclusions of these reviews are reflected in the practice variation between countries (9) and among paediatric EDs (8).

Interesting and conflicting views regarding the use of probiotics are highlighted by a 2010 Cochrane Review that included 63 studies and a total of 8014 participants (21). Despite the large number of studies, the authors concluded that 'more research is needed to guide the use of particular probiotic regimens in specific patient groups' (21). Currently, only 15% of North American PEM physicians report administering probiotics to children with gastroenteritis (9) with many indicating that they do not feel the evidence is sufficiently compelling to routinely recommend their use (9). Further, the endpoints evaluated in the systematic reviews to date (e.g. duration of diarrhoea, number of stools on day 3) are not felt to be clinically relevant (9). Consequently, current usage at discharge from Canadian EDs ranges from 0% to 17% (8).

### Why it is important to do this overview

Conducting an overview on the currently available treatment options for AGE is urgently needed to synthesize the evidence regarding treatments of one of the most common diseases of childhood. The aim of this overview is to provide the most up to date evidence on approaches to treating children with AGE and to help clinicians in their evidence-based decision-making when providing care to such patients. Our evidence synthesis has the potential to result in more consistent and appropriate management of children with AGE.

### Objectives

This overview is a critical evaluation of the evidence available in the *Cochrane Database of Systematic Reviews* (CDSR) regarding the efficacy and safety of treatments for AGE in children.

### Methods

#### Criteria for considering reviews for inclusion

All Cochrane reviews of clinical trials on the following treatments of AGE in children were potentially eligible for inclusion: ORT, anti-emetics and probiotics. We excluded reviews of other topics including antibiotic or nosocomial diarrhoea, persistent (chronic) diarrhoea and the prevention of gastroenteritis.

#### Search methods for the identification of reviews

For this overview, we intended to include only reviews of randomized clinical trials published in the CDSR (Cochrane reviews); however, owing to an absence of eligible reviews on interventions/outcomes specified a priori, we expanded to include a non-Cochrane review (see Results). Thus, we searched the following databases in May 2012 employing a search strategy (see Appendix) developed by a research

librarian (AM) that covered Medline, Cochrane Library, Embase, Global Health and PubMed. Two reviewers (DP, MM) independently screened the results of the literature search. The full texts of potentially relevant articles were retrieved, independently screened and assessed for inclusion. Any disagreements were resolved through discussion.

### Type of outcome measures

Outcomes specified, a priori, for inclusion in this overview were:

- Rate of admission to the hospital
- Length of stay in hospital
- Rate of return visits
- Administration of intravenous (IV) therapy due to failure of ORT
- Adverse events
- Dysnatremia (for comparisons involving IV therapy)

Other outcomes, such as mean duration of diarrhoea, stool frequency, weight gain and fluid or sodium intake were considered to be less clinically meaningful. As such, they were not evaluated in this overview.

### Data collection and analysis

One reviewer (MO) extracted the following data from each included review: search methods, inclusion criteria (population, intervention, comparison and outcomes), methodological quality of the included trials and numerical results. A second reviewer (DP) independently verified extracted data. For the purposes of this overview, we extracted only data related to paediatric trials (i.e. patients under 18 years of age).

For continuous data, mean differences (MD) with 95% confidence interval (CI) were used. For dichotomous data, risk ratios (RR) with 95% CI were used in two reviews (17, 21); owing to frequent zero event rates, risk difference (RD) rather than RR was used in one review (13). Review Manager 5 (22) was used to conduct additional analyses that were not included in the original reviews.

To quantify the degree of the treatment effect for dichotomous outcomes that were statistically significant, we calculated the number needed to treat (NNT) using the following formula:

1. For harmful outcomes  $NNT = 1/[\text{control group risk} (1 - RR_{\text{harm}})]$
2. For beneficial outcomes  $NNT = 1/[\text{control group risk} (RR_{\text{benefit}} - 1)]$
3.  $NNT = 1/|RD|$

where  $RR_{\text{harm}}$  and  $RR_{\text{benefit}}$  are risk ratios for harmful and beneficial outcomes, respectively.

### Results

#### Description of included reviews

Our search identified three Cochrane systematic reviews (13, 17, 21). However, the review (21)

**Table I.** Characteristics of included reviews

Title of review	Date assessed as up to date	Population	Intervention	Trials	Participants	Outcomes included in present overview
Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children (13)	March 2006*	Children (<18 years) with dehydration secondary to acute GE	ORT orally or via nasogastric tube versus IVT	17	1811	Length of hospital stay Incidence of hyponatremia Incidence of hypernatremia Complications
Anti-emetics for reducing vomiting related to acute gastroenteritis in children and adolescents (17)	November 2010	Children (<18 years) with vomiting and confirmed diagnosis of GE	Any anti-emetics, any route versus placebo, vehicle or nothing	7	1020	Rate of admission to the hospital Rate of IV rehydration Revisit rate Adverse events
Probiotics for treating acute infectious diarrhoea (21)	August 2010	Adults and children with acute diarrhoea caused by an infectious agent	Probiotics versus placebo or no probiotics	63 (55)†	8014 (6489)†	Adverse events
A meta-analysis and systematic review on the effect of probiotics in acute diarrhoea (28)	Not reported‡	Children with diarrhoea	Any probiotic versus placebo	20	3867	Duration of hospitalization

\*This review was declared as stable by The Cochrane Collaboration, i.e. new trials are unlikely to change the conclusion and research on this specific question is not warranted; therefore, authors will no longer update this review.

†Data related to trials with children only in brackets.

‡Review authors did not report date of search; article was revised in October 2011.

GE, gastroenteritis; ORT, oral rehydration therapy; IV, intravenous; IVT, intravenous rehydration therapy.

evaluating the use of probiotics for treating AGE did not assess any of the pre-specified outcomes; consequently, as described above, we expanded our search. The expanded database search identified 10 additional potentially relevant reviews on probiotics (23–32). Of these, we identified a single non-Cochrane review (28) that met study eligibility criteria, and was deemed to be the most comprehensive and up-to-date one. In total, the four reviews (13, 17, 21, 28) included in our overview contained 95 unique randomized controlled trials and 12 478 participants. Eighty-seven of the randomized controlled trials included subjects < 18 years of age ( $N = 10\,954$ ; Table I).

#### Search methods used in the included reviews

The three Cochrane reviews (13, 17, 21) searched Medline, Embase and Central for potentially eligible randomized clinical trials; in addition, two of them (13, 21) searched the Cochrane Infectious Disease Group Specialized Register and one (13) searched LILACS. All three Cochrane reviews (13, 17, 21) sought unpublished literature. The non-Cochrane review (28) reported searching PubMed, Web of Science (ISI), Scopus and Cochrane databases.

#### Interventions in included reviews

All reviews included only randomized controlled trials. One Cochrane review (13) compared oral to IV rehydration therapies. All included trials employed oral rehydration solutions containing glucose or

dextrose (one trial used a combination of glucose and fructose), with sodium, potassium and chloride, as well as with either citrate or bicarbonate.

One Cochrane review (17) included comparisons of anti-emetics given orally (ondansetron), rectally (dimenhydrinate) or IV (ondansetron) with placebo, as well as comparisons of two active anti-emetic treatments (ondansetron versus dexamethasone, ondansetron versus metoclopramide).

In two of the reviews (21, 28) probiotics administered orally were compared to placebo or no probiotics (oral rehydration fluid, non-fermented lactogen-2, inulin, standard treatment, trimethoprim-sulfamoxazole); studies on any specific probiotic agent were considered for inclusion. The most common probiotics tested were *Lactobacillus Casei* strain GG (19 studies in Cochrane review and eight studies in non-Cochrane review), *Saccharomyces boulardii* (10 and four trials, respectively), and *Lactobacillus acidophilus* (10 and four, respectively). Other organisms tested included *Enterococcus LAB*, *Saccharomyces thermophilus* and *Lactobacillus bulgaricus*.

#### Population in the included reviews

The Cochrane review comparing ORT and IV rehydration (13) included both inpatient and outpatient children up to 18 years of age with dehydration caused by AGE. Of the 18 trials contributing to this review, two did not specify age of participants; the other trials included patients from 1 day to 17 years of age.

The Cochrane review on anti-emetics (17) included trials involving children and adolescents under 18 years of age who presented with vomiting and a clinical diagnosis of gastroenteritis. The age of participants was between 5 months and 12 years.

The Cochrane review on probiotics (21) included studies involving adults as well as children and infants with acute diarrhoea of presumed or proven infectious aetiology. Of the 63 trials included in this review, 55 included patients less than 18 years of age, five recruited only adults and three did not state the age of the participants. Among the 55 trials that included children, 23 specified the ages of the included patients, which ranged from 1 month to 12 years.

Finally, the non-Cochrane review on probiotics (28) included 20 trials involving children with diarrhoea. There was no information provided in the review about the age of the patients in the included studies.

### Outcomes in included reviews

Three Cochrane reviews (13, 17, 21) provided pre-defined outcome lists, while the non-Cochrane review on probiotics (28) did not pre-specify outcomes.

The Cochrane review (13) comparing oral with IV rehydration therapies specified failure of rehydration or failure to maintain hydration after initial rehydration, and death as primary outcomes. Secondary outcomes were weight gain, length of hospital stay for inpatients, hypernatremia, hyponatremia, duration of diarrhoea, total fluid intake, sodium intake and sodium levels and complications and adverse events.

The Cochrane review of anti-emetics for reducing vomiting related to AGE (17) assessed time taken from the first administration of the treatment until cessation of vomiting as a primary outcome. Secondary outcomes included parental satisfaction (questionnaire or interview), number of participants who required hospitalization, number of participants who required IV rehydration, mean number of episodes of vomiting, proportion of participants with cessation of vomiting, number of participants who revisited an ED, and number of participants who resumed oral rehydration (i.e. patients who were able to tolerate oral hydration). Adverse events were documented.

In the Cochrane review comparing probiotics with placebo or no probiotics (i.e. oral rehydration fluid, non-fermented lactogen-2, inulin, standard treatment, trimethoprim - sulfamethoxazole) (21), the primary outcomes were duration of diarrhoea, diarrhoea lasting  $\geq 4$  days and stool frequency on day 2 after intervention. Secondary outcomes were diarrhoea lasting  $\geq 3$  days and stool frequency on day 3 after the intervention. None of these outcomes fulfilled criteria for inclusion in this overview. Consequently, as described above, a non-Cochrane review comparing probiotics with placebo (28) was identified which assessed the duration of diarrhoea, fever, hospitalization, vomiting and the number of stools per day. Review authors did not specify which of these was the primary outcome.

### Methodological quality of trials included in reviews

The Jadad 5-point scale (33) was used to evaluate methodological quality of included trials in the review comparing ORT with IV rehydration (13) and in the non-Cochrane review on probiotics (28). This tool assesses randomization (0–2 points), double blinding (0–2 points) and description of withdrawals and dropouts (0–1 points). The quality of the studies ranged from 1 to 5 (median 4.5) in the review of probiotics (28). The nature of the intervention (oral versus IV) in the rehydration therapy review (13) did not allow trials to be double blinded, hence the maximum Jadad score for included trials was 3; the quality of the included trials ranged from 0 to 3 (median 2).

The reviews on anti-emetics (17) and probiotics (21) employed different aspects of the risk of bias tool (34). All domains (i.e. sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias) were evaluated in the review on anti-emetics (17). In this review, incomplete outcome data and other sources of bias were considered as high risk in four of seven included trials. In addition, review authors identified other sources of bias that are associated with trial conduct (e.g. poor screening methodologies, baseline imbalance, ad hoc method of recruitment). In the Cochrane review on probiotics, (21) sequence generation, allocation concealment, blinding and incomplete outcome data were assessed (Table II). Study authors reported that there was an unclear risk of bias with respect to sequence generation and allocation concealment in 28 and 34 of the trials (total  $N = 55$ ), respectively; majority of the studies were deemed low risk of bias regarding blinding and incomplete outcome data (28 and 42 of total  $N = 55$ , respectively).

### Effects of intervention

#### Oral versus IV rehydration for treating dehydration caused by gastroenteritis

Seventeen trials that were included in one review (13) compared the efficacy of oral versus IV rehydration therapy for treating dehydration in children with AGE. There were 1811 patients included; sample sizes ranged from 24 to 470 (median 81.5; Table III). Children who received ORT spent less time in hospital compared with those who received IV therapy (MD =  $-1.20$  days, 95% CI  $-2.38$  to  $-0.02$ ); however, there was substantial heterogeneity among trials ( $I^2 = 95\%$ ). The review authors explored heterogeneity and found one study which included neonates and was conducted in Mexico in the 1980s to be an outlier. When removed from the analysis the result for length of hospital stay was no longer statistically significant (MD =  $-0.34$  days, 95% CI  $-0.77$  to  $0.08$ ). The review authors discussed other sources of heterogeneity between studies, focusing on rehydration solutions employed and their rates and routes of administration.

**Table II.** Summary of risk of bias assessment for trials included in (21) and (17)

Risk of bias dimension	Low risk of bias N (%)	Unclear risk of bias N (%)	High risk of bias N (%)	Number of trials assessed
Sequence generation	26 (42)	29 (47)	7 (11)	62
Allocation concealment	20 (32)	35 (57)	7 (11)	62
Blinding	33 (53)	18 (28)	12 (19)	62
Incomplete outcome data	45 (73)	4 (6)	13 (21)	62
Selective reporting	7 (100)	0 (0)	0 (0)	7
Other sources of bias	1 (14)	2 (29)	4 (57)	7

**Table III.** Oral rehydration therapy (any solution) versus intravenous therapy

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
Length of hospital stay (days):				
<b>Overall</b>	<b>6 (526)</b>	<b>MD = -1.20 (-2.38 to -0.02)*</b>	<b>95</b>	—
Outlier removed	5 (326)	MD = -0.34 (-0.77 to 0.08)	55	—
Incidences of hyponatremia:				
Inpatients	2 (248)	RD = 0.01 (-0.13 to 0.15)	67	—
Incidences of hypernatremia:				
Inpatients	8 (1002)	RD = 0.00 (-0.01 to 0.01)	0	—
Outpatients	2 (60)	RD = 0.00 (-0.09 to 0.09)	0	—
Complications:				
Paralytic ileus†	2 (670)	RD = 0.02 (0.00 to 0.05)	44	—
<b>Phlebitis</b>	<b>5 (877)</b>	<b>RD = -0.02 (-0.04 to -0.01)*</b>	<b>0</b>	<b>50 (25 to 100)</b>
Peri-orbital oedema	7 (844)	RD = 0.00 (-0.02 to 0.02)	7	—
Abdominal distention	1 (470)	RD = 0.02 (0.00 to 0.04)	N/a	—
Seizures	6 (877)	RD = -0.01 (-0.03 to 0.01)	0	—

\*Favours ORT.

†This result was statistically significant (favours IV rehydration) when analysed using a fixed effects model (RD = 0.03, 95% CI 0.01 to 0.05).

NNT, number needed to treat.

Children receiving ORT had lower likelihood of developing phlebitis than children receiving IV therapy (RD = -0.02, 95% CI -0.04 to -0.01; NNT = 50, 95% CI 25–100). Paralytic ileus was more common in children receiving ORT; the result was statistically significant when analysed using a fixed effects model (RD = 0.03, 95% CI 0.01–0.05) but not when a random effects model was employed. The incidences of peri-orbital oedema, abdominal distention and seizures were similar between groups. Additionally, there were no significant differences between groups in the incidence of developing hyponatremia or hypernatremia.

#### Anti-emetics for reducing vomiting related to AGE

The review of anti-emetics (17) included seven studies and 1020 patients with sample sizes ranging from 36 to 243 (median 109).

**Oral ondansetron:** Four studies compared orally administered ondansetron with placebo (Table IV). Children who received oral ondansetron had lower hospital admission rates to the ED and lower rates of IV rehydration during their ED stay compared with children receiving placebo (RR = 0.40, 95% CI 0.19–0.83; NNT = 17, 95% CI 13–60 and RR = 0.41, 95% CI 0.29–0.59; NNT = 5, 95% CI 4–8, respectively). Up to 72 hours following discharge from the ED, children who received oral ondansetron had

lower risk of receiving IV rehydration based on the analyses using both worst-best and best-worst case scenarios (RR = 0.52, 95% CI 0.38–0.71; NNT = 6, 95% CI 5–10 and RR = 0.57, 95% CI 0.42–0.76; NNT = 7, 95% CI 5–12, respectively). There was no difference in rates of hospital revisits up to 72 hours following ED discharge. A single study reported urticaria in one patient receiving placebo and another study reported a macular rash in one patient receiving ondansetron. Three studies reported higher frequency of diarrhoea in the ondansetron group (numerical data not available).

**Intravenous ondansetron:** Two three-arm trials included comparisons of IV ondansetron to placebo (Table V). Patients receiving IV ondansetron had lower hospital admission rates to the ED than patients receiving placebo (RR = 0.21, 95% CI 0.05–0.93; NNT = 7, 95% CI 6–70). One trial reported no significant adverse events; the second trial reported that there were more episodes of diarrhoea in the first 24 hours in the ondansetron group but did not provide numbers.

The efficacy of IV ondansetron was compared with IV dexamethasone in a single study (Table VI). There was no statistically significant difference between treatment groups in the rate of hospital admission to the ED. The investigators did not report any significant side effects.

**Table IV.** Oral ondansetron (weight-dependent dose) versus placebo

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
Rate of admission to hospital (during ED stay)	3 (465)	RR = 0.40 (0.19 to 0.83) <sup>a</sup>	17	17 (13 to 60)
Rate of admission to hospital (up to 72 h following discharge from ED stay):				
Best-worst case scenario	3 (461)	RR = 0.60 (0.34 to 1.04)	49	—
Worst-best case scenario	3 (461)	RR = 0.73 (0.43 to 1.22)	0	—
<b>Rate of IV rehydration (during ED stay)</b>	<b>3 (465)</b>	<b>RR = 0.41 (0.29 to 0.59)*</b>	<b>0</b>	<b>5 (4 to 8)</b>
Rate of IV rehydration (up to 72 h following discharge from ED stay):				
<b>Best-worst case scenario</b>	<b>3 (461)</b>	<b>RR = 0.52 (0.38 to 0.71)*</b>	<b>0</b>	<b>6 (5 to 10)</b>
<b>Worst-best case scenario</b>	<b>3 (461)</b>	<b>RR = 0.57 (0.42 to 0.76)*</b>	<b>0</b>	<b>7 (5 to 12)</b>
Revisit rate	3 (457)	RR = 1.09 (0.66 to 1.79)	28	—

\* Favours ondansetron.

ED, emergency department; IV, intravenous; NNT, number needed to treat.

**Table V.** Intravenous ondansetron versus placebo\*

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
<b>Hospital admission rate during ED stay</b>	<b>1 (90)</b>	<b>RR = 0.21 (0.05 to 0.93)<sup>†</sup></b>	<b>Na</b>	<b>7 (6 to 70)</b>
IV rehydration rate	1 (24)	RR = 7.00 (0.40 to 122.44)	Na	—

\*The investigators indicated that they 'did not find any significant side effects'.

<sup>†</sup>Favours IV ondansetron.

ED, emergency department; IV, intravenous; NNT, number needed to treat.

A single trial compared IV ondansetron with metoclopramide (Table VII). Episodes of diarrhoea in the first 24 hours were reported in both groups with no significant difference between groups (numerical data not available).

**Dimenhydrinate:** The review included one study comparing use of dimenhydrinate with placebo (Table VIII). There was no significant difference between groups in hospital admission rate to the ED. Similarly, there were no statistically significant differences in the risk of developing sedation or a rash.

### Probiotics for acute infectious diarrhoea

Two reviews (21, 28) compared probiotics to placebo or no probiotics for AGE. A Cochrane review (21) included 55 studies with children. Sample size ranged from 25 to 662 children (median 93). A descriptive adverse events summary indicated that no adverse events were attributed to the use of probiotics. Although vomiting was recorded in several studies, review authors suggested that this was a symptom of illness rather than an effect of the probiotics. None of the outcomes analysed in this Cochrane review (21) fulfilled our pre-specified inclusion criteria (Table IX).

The non-Cochrane review comparing probiotics with placebo (28) included 20 trials involving 3867 paediatric patients. Sample sizes ranged from 69 to 913 (median 98.5). One outcome (duration of hospitalization) analysed in the review contributed to this overview (Table III). A shorter hospitalization time (days) was observed in patients treated with probiotics compared with placebo (MD = -1.12, 95% CI -1.16 to -0.38). The result was statistically significant but reviewers indicated high heterogeneity as determined by Cochrane Q test ( $p < 0.0001$ ). Authors reported use of random effects model to reflect high heterogeneity, however they did not explore the sources of this heterogeneity.

## Discussion

### Summary of main results

#### Oral versus IV rehydration for treating dehydration due to AGE in children

Hartling et al. (13) included 17 randomized controlled trials in their review comparing ORT versus IV rehydration for treating dehydration due to AGE. The review authors concluded that children should be offered ORT initially as there are no important

**Table VI.** Intravenous ondansetron versus dexamethasone\*

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
Hospital admission rate during ED stay	1 (93)	RR = 0.29 (0.06 to 1.33)	Na	—

\* The investigators indicated that they 'did not find any significant side effects'.

ED, emergency department; NNT, number needed to treat.

**Table VII.** Intravenous ondansetron versus metoclopramide

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
IV rehydration rate during first 24 h	1 (24)	RR = 3.00 (0.36 to 24.92)	Na	—

IV, intravenous; NNT, number needed to treat.

**Table VIII.** Dimenhydrinate versus placebo

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
Hospital admission rate during the ED stay	1 (209)	RR = 0.75 (0.34 to 1.63)	Na	—
Adverse events:				
Sedation	1 (200)	RR = 1.17 (0.67 to 2.05)	Na	—
Rash	1 (200)	RR = 0.96 (0.06 to 15.15)	Na	—

ED, emergency department; NNT, number needed to treat.

clinical differences between the two therapies. The review demonstrated shorter hospital stays with ORT; however, this finding was sensitive to an outlying study involving neonates and the result was no longer significant when this trial was removed from the analysis. The review authors noted a number of differences across the included studies. For example, although all trials reported on the review authors' primary outcome of interest—the failure to rehydrate using ORT—the definition of treatment failure varied significantly between studies. In addition, both hospital inpatients and outpatients were included resulting in a heterogeneous population. Although the included studies originated from both high- and low-income countries, the results were consistent among different populations (i.e. nutritional status, aetiologic organisms). Lastly, while most of the included studies focused on children less than 5 years of age, children in shock or with severe dehydration were generally excluded. Although most trials did not systematically report adverse events and there were no significant differences in the development of hyponatremia or hypernatremia between groups, phlebitis did occur more often in the IV group and paralytic ileus more often in the ORT group. Consequently, in the appropriate context, these results indicate that oral rehydration should be the initial therapy in children with AGE and mild-to-moderate dehydration.

#### Anti-emetics for reducing vomiting related to AGE in children and adolescents

The review published by Fedorowicz (17) assessed the safety and effectiveness of anti-emetics for AGE-related vomiting. Overall, anti-emetic agent administration significantly increased the likelihood that children would stop vomiting, reduced the need for IV therapy during the ED stay and reduced the immediate hospital admission rate. Although ondansetron was associated with an increased rate of diarrhoea, there was no difference in the hospitalization rate within 72 hours of ED discharge. As such, the use of ondansetron might not be the ideal choice in children whose predominant symptom is diarrhoea.

While guidelines are now beginning to endorse the use of ondansetron (19) in children with AGE in the ED, their optimal use requires further refinement. Areas that require further research include use in the outpatient setting (i.e. non-ED) as well as use in children with none/minimal degrees of dehydration. In addition, although some clinicians prescribe the use of multiple dose ondansetron (i.e. following ED discharge) (8), this practice is not supported by the evidence to date (35).

Recently, some concerns have been published regarding the risk of developing prolongation of the QT interval in patients with potential electrolyte abnormalities who receive IV ondansetron (36). A review of the available literature does not seem to indicate that any concerns exist with the use of single dose oral ondansetron in otherwise healthy children (S. Freedman, personal communication).

#### Probiotics for the treatment of AGE

The systematic review by Salari et al. (28) on probiotic use in AGE included 20 paediatric randomized controlled trials. While they evaluated many outcomes, the only one that was congruent with the goals of our overview was duration of hospitalization. When compared to placebo, they determined that probiotic use reduced mean hospitalization time by 1.12 days. An array of different probiotic organisms (*Lactobacillus species*, *S. boulardii* and *Bifidobacterium*), doses (one billion colony-forming units (CFUs) per day to 10 billion CFUs per day), treatment durations (3–14 days), study populations, designs, settings and aetiologies were included in this review. This variability makes it extremely difficult to draw any broad sweeping generalizable conclusions and hence it is not possible to generate a clear practice recommendation. Further, results may not be applicable to all children, in particular those who are immunocompromised because of the possibility of probiotic administration resulting in bacteremia in this subgroup. Additional concerns revolve around the funding of the majority of the studies by the manufacturers of the study agents (37–39).

**Table IX.** Probiotics versus placebo

Outcome	Studies (participants)	Effect estimate (95% CI)	I <sup>2</sup> (%)	NNT (95% CI)
Duration of hospitalization (days)	10 (≤1932)*	MD = -1.12 (-1.16 to -0.38)†	‡	—

\*Favours probiotics.

†Authors did not provide exact number of patients contributing to this outcome.

‡Review authors did not calculate I<sup>2</sup>.

NNT, number needed to treat.

### Limitation of the overview

#### Oral versus IV rehydration for treating dehydration due to gastroenteritis in children

In the included review, the 17 eligible trials often were of small sample size and low quality (0–3 on Jadad scale). The review included both randomized controlled trials and two quasi-randomized studies. None of the trials were double-blinded because of the nature of the intervention. Furthermore, allocation concealment was unclear in all but two trials. Five of the included trials were funded by pharmaceutical companies, which introduces an additional potential source of bias. The Cochrane review has not been updated since 2006 because the results are unlikely to change with additional research; however, a more recent non-Cochrane review (40) including the latest evidence reported results that were similar to those described above.

#### Anti-emetics for reducing vomiting related to AGE in children and adolescents

Most of the included studies in this review were recent, of good quality, and adhered to the current guidelines on the conduct of randomized controlled trials. However, not all of the included studies fully addressed the outcome measures that were deemed clinically relevant. The participant age range was 5 months to 12 years, which is somewhat limited in scope. Further, the eligibility criteria varied between studies in terms of severity of dehydration and the number of vomiting episodes required. The majority of participants enrolled were suffering from mild-to-moderate dehydration, with severely dehydrated children being excluded. The definition of AGE also varied somewhat among the studies (e.g. requirement for diarrhoea). In some studies, a single dose of the intervention medication was provided while in others multiple dose regimens were employed. Furthermore, the intensity of the described ORT protocols followed varied between studies. The funding of several of the studies by the pharmaceutical industry must be considered when interpreting the aforementioned findings.

#### Probiotics for the treatment of AGE

Although a current Cochrane review on the use of probiotics in children that includes 55 paediatric trials is available, we were unable to include its results in our overview as the outcomes measured were not deemed to be clinically relevant. This finding and

the general use of diverse outcome measures in AGE studies (41) is a general impediment for successful knowledge translation to occur and highlights the need for consistency in outcome measures in AGE research.

Based on a non-Cochrane review, the data regarding the impact of probiotic administration on the duration of hospitalization indicated a statistically significant reduction associated with probiotic use. However given the high degree of heterogeneity identified, it is unclear whether the observed decrease reflects a true and consistent finding, or is a result of over-representation of one or few trials.

### Conclusions

#### Implications for practice

There are no important clinical differences (e.g. length of hospital stay, adverse effects) between children who receive ORT and those administered IV rehydration therapy. Given that ORT is less invasive than IV rehydration, and avoids the potential complications associated with venous cannulation (e.g. phlebitis), it is the currently recommended first choice for rehydration in AGE.

As most children with AGE do not require IV rehydration, oral ondansetron should be considered as a first line anti-emetic agent amongst children with dehydration and significant vomiting as it lowers both hospital admission and IV rehydration rates. Intravenous (IV) ondansetron use is also associated with lower hospital admission rates to the ED, and should be considered for use in children with AGE who require IV rehydration.

Probiotics have been shown to reduce hospitalization duration by over 24 hours. The clinical and financial implications that this benefit incurs could be significant at both a patient- and hospital-level. Although the existing evidence for probiotics use in AGE appears to favour its use, the size of the effect varies across studies. As such, it is unclear exactly which probiotic agent, at what dose, and for what duration treatment should be provided. At this time, current evidence would suggest that *Lactobacillus sp.* may be considered for hospitalized children, but the optimal dosing and duration of treatment remains unclear. Given that there are no known interactions between probiotics and other medications, they appear to be a safe and effective adjunct treatment of AGE amongst hospitalized children (42, 43). However, outpatient studies are urgently needed.

## Implications for research

As ORT appears to be the optimal route of rehydration for the majority of children, research aimed at enhancing its uptake and adoption continues to be a priority. Potential areas to consider include improving ORT taste and changing both healthcare providers' as well as public perceptions of its acceptability.

As ondansetron use has recently been proven to be both clinically (18, 19) and economically (3) advantageous, there has been a dramatic increase in its use in select developed countries (44). However, since the majority of studies to date were performed in higher income countries, and considering the cost of ondansetron, further research into its use in other settings is required.

Among the relevant studies, there is little consistency in the choice of probiotic formulation (e.g. strain of bacteria), dosage and duration of treatment. As such, despite the knowledge that probiotics may shorten duration of hospitalization for AGE, clinicians still lack guidance regarding which probiotic to recommend. Currently, it would appear that benefit is most likely to result from use of the formulations that include *Lactobacillus sp* and *S. boulardii*. However, there is an urgent need for studies focusing on the optimal dose and duration of therapy. Lastly, given that most healthcare plans do not include the cost of probiotics, a cost-benefit analysis could help guide policymakers regarding its inclusion in provincial or national formularies.

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## Contribution of authors

All authors contributed in the preparation of this overview. SF wrote the Background section. SA and SG wrote the Discussion and Conclusion sections. SA prepared the Abstract. MO wrote Plain Language Summary, Methods, and Results. LH critically reviewed all sections and coordinated the project. All authors critically reviewed the manuscript and approved the final version submitted.

## Declaration of interest

Dr Stephen Freedman is currently conducting a study employing a study product (ondansetron/placebo) provided by GlaxoSmithKline. This work was completed in part with funding from a Knowledge Synthesis Grant from the Canadian Institutes of Health

Research. Dr Lisa Hartling holds a New Investigator Salary Award from the Canadian Institutes of Health Research.

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## Appendix

### Search summary

Review	Date searched	Number retrieved	After duplicate removal
Medline	2 May 2012	975	976
Cochrane Library	2 May 2012	527	506
Embase	2 May 2012	2266	1811
Global Health*	2 May 2012	253	128
PubMed last 180 days*	2 May 2012	8	1
Total		4029	3419

\*Additional suggested databases.

**Database:** Medline via Ovid <1946 to Present>

**Search Title:** Gastroenteritis KT Grant 1.1—expansion of text words—SRs Only — Medline—April 4, 2012—AM

**Date Searched:** April 5, 2012 (initial); May 2, 2012 (final)

**Results:** 1016; after Ovid duplicate removal function: 975

**Terms for Gastroenteritis:**

1. exp Gastroenteritis/
2. Rotavirus/
3. Rotavirus Infections/
4. exp Norovirus/
5. exp Diarrhea/
6. Vomiting/
7. Dehydration/
8. gastroenterit\*.tw.
9. (diarrhea or diarrhoea).tw.
10. vomit\*.tw.
11. dehydrat\*.tw.
12. gastritis.tw.

**13. or/1-12** [combination of MeSH and text words for Gastro] (284,625)

**Terms for Oral, IV, and Nasogastric Rehydration:**

14. exp fluid therapy/
15. Rehydration Solutions/

- 
16. Administration, Oral/  
 17. Infusions, Intravenous/  
 18. Enteral Nutrition/  
 19. Infusions, Parenteral/  
 20. exp Parenteral Nutrition/  
 21. Parenteral Nutrition Solutions/  
 22. rehydrat\*.tw.  
 23. (ORT or ORS).tw.  
 24. ((fluid or IV) adj3 therap\*).tw.  
 25. (water adj2 electrolyte adj2 balance).tw.  
 26. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 therap\*).tw.  
 27. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 infusion\*).tw.  
 28. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 drip\*).tw.  
 29. (nasogastric\* or (NG adj3 tube\*)).tw.
- 

**30. or/14-29** [combination of MeSH and text words for rehydration, oral or other] (262,447)

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*Terms for Treatment with Antiemetics:*

31. exp Antiemetics/  
 32. exp Dopamine Antagonists/  
 33. exp Serotonin Antagonists/  
 34. exp Cholinergic Antagonists/  
 35. exp Histamine Antagonists/  
 36. exp Benzodiazepines/  
 37. exp Adrenal Cortex Hormones/  
 38. exp Cannabinoids/  
 39. (antiemetic\* or anti-emetic\*).tw.  
 40. anti-vomit\*.tw.  
 41. ((dopamine or serotonin or cholinergic or histamine) adj1 antagonist\*).tw.  
 42. benzodiazepine\*.tw.  
 43. "adrenal cortex hormone\*".tw.  
 44. cannabinoid\*.tw.  
 45. ("5-HT3" or "5-hydroxytryptamine").tw.
- 

**46. or/31-45** [MeSH and textwords for antiemetics] (599,299)

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*Terms for Treatment with Probiotics:*

47. Probiotics/  
 48. exp Lactobacillaceae/  
 49. exp Lactococcus/  
 50. exp Enterococcaceae/  
 51. exp Streptococcaceae/  
 52. exp Saccharomyces/  
 53. Probiotic\*.tw.  
 54. Lactobacill\*.tw.  
 55. Lactococc\*.tw.  
 56. Enterococc\*.tw.  
 57. Streptococc\*.tw.  
 58. Saccharomyc\*.tw.  
 59. bifidobacter\*.tw.  
 60. (microbi\* adj3 supplement\*).tw.  
 61. ("L. GG" or "L.GG").tw.
- 

**62. or/47-61** [MeSH and textwords for probiotics] (216,218)

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**63. or/30,46,62** [combination of treatments of interest: ORT, antiemetics, probiotics] (1,051,322)

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**64. and/13,63** [combination of gastro terms + treatments of interest] (40,336)

---

*Terms for Child (<= 18 years) Population:*

65. exp Child/  
 66. exp Infant/  
 67. exp pediatrics/  
 68. Adolescent/  
 69. Minors/  
 70. (infant\* or child\* or adolescen\* or teen\* or youth\* or young or p?ediatric\* or juvenile\*).tw. (1,425,360)
- 

**71. or/65-70** [combination of MeSH and text terms for children] (2,998,700)

---

**72. and/64,71** [combination of gastro terms + treatment terms + children] (13,104)

---

*Filter for SRs:*

73. meta analysis.mp.pt.  
 74. review.pt.  
 75. search\*.tw.
- 

**76. or/73-75** [HIRU SR filter to max sensitivity and specificity] (1,820,782)

---

**77. and/72,76** [combination of gastro terms + treatment terms + children + SRs] (1,733)

---

78. limit 77 to humans (1,724)  
 79. limit 78 to yr="2000 -Current" (1,016)  
 80. remove duplicates from 79 (975)
- 

*Database Searched: Evidence-Based Medicine Reviews via Ovid*

**Cochrane Database of Systematic Reviews <2005 to November 2011>, Database of Abstracts of Reviews of Effects <4th Quarter 2011>, Health Technology Assessment <4th Quarter 2011>, NHS Economic Evaluation Database <4th Quarter 2011>**  
*Search Title: Gastroenteritis KT Grant 3.0—SRs Only | Cochrane Library—April 16, 2012—AM*  
*Date Searched: April 18, 2012 (initial); May 2, 2012 (final)*

**Results: 527**

---

*Text terms for Gastroenteritis:*

1. gastroenterit\*.mp.  
 2. (diarrhea or diarrhoea).mp.  
 3. vomit\*.mp.  
 4. dehydrat\*.mp.  
 5. gastritis.mp.  
 6. (rotavirus or rota-virus).mp.  
 7. norovirus.mp.
- 

**8. or/1-7** [combination of text words for Gastroenteritis] (2,783)

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*Text terms for Oral, IV, Nasogastric Rehydration*

9. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 therap\*).mp.  
 10. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 infusion\*).mp.  
 11. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 drip\*).mp.  
 12. rehydrat\*.mp.  
 13. (ORT or ORS).mp.  
 14. (water adj2 electrolyte adj2 balance).mp.  
 15. (nasogastric\* or (NG adj3 tube\*)).mp.  
 16. ((parenteral or enteral) adj3 (nutrition or solution\*)).mp.  
 17. (oral adj5 admin\*).mp.
- 

**18. or/9-17** [combination of text words for rehydration, oral or other] (4,260)

---

*Text terms for Treatment with Antiemetics:*

19. (antimetic\* or anti-emetic\*).mp.  
 20. anti-vomit\*.mp.  
 21. ((dopamine or serotonin or cholinergic or histamine) adj3 antagonist\*).mp.
-

22. benzodiazepine\*.mp.  
 23. "adrenal cortex hormone\*".mp.  
 24. cannabinoid\*.mp.  
 25. ("5-HT3" or "5-hydroxytryptamine").mp.

**26. or/19-25** [combination of text words for antiemetics] (1,416)

*Text terms for Treatments with Probiotics:*

27. probiotic\*.mp.  
 28. lactobacill\*.mp.  
 29. Lactococc\*.mp.  
 30. Enterococc\*.mp.  
 31. Streptococc\*.mp.  
 32. Saccharomyc\*.mp.  
 33. bifidobacter\*.mp.  
 34. (microbi\* adj3 supplement\*).mp.  
 35. (microbi\* adj5 supplement\*).mp.  
 36. ("L. GG" or "L.GG").mp.

**37. or/27-36** [combination of text words for probiotics] (429)

**38. or/18,26,37** [combination of treatments of interest: ORT, antiemetics, probiotics] (5,682)

**39. and/8,38** [combination of gastro terms and treatment terms] (1,198)

*Terms for Child (≤ 18 years) Population:*

40. (infant\* or child\* or adolescen\* or teen\* or youth\* or young or p?ediatric\* or juvenile\* or minor\*).mp. (13,360)

**41. and/39-40** [combination of gastro + treatments + child] (781)

42. limit 41 to yr="2000 -Current" [Limit not valid in DARE; records were retained] (768)  
 43. limit 42 to humans [Limit not valid in CDSR,DARE; records were retained] (766)  
 44. limit 43 to protocols [Limit not valid in DARE,CLHTA,CLEED; records were retained] (243)

**45. 43 not 44** (527)

*Database: Embase via Ovid <1980 to Present>*

*Search Title: Gastroenteritis KT Grant 2.0—SRs Only | Embase—April 16, 2012—AM*

*Date Searched: April 17, 2012 (initial); May 2, 2012 (final)*

*Results: 2292; after Ovid duplicate removal 2266*

*Terms for Gastroenteritis:*

1. exp gastritis/  
 2. exp Rotavirus/  
 3. Rotavirus infection/  
 4. Norovirus/  
 5. exp diarrhea/  
 6. dehydration/  
 7. gastroenterit\*.tw.  
 8. (diarrhea or diarrhoea).tw.  
 9. vomit\*.tw.  
 10. dehydrat\*.tw.  
 11. gastritis.tw.

**12. or/1-11** [combination of index and text words for Gastroenteritis] (292,035)

*Terms for Oral, IV, and Nasogastric Rehydration:*

13. exp fluid therapy/  
 14. exp antidiarrheal agent/  
 15. oral drug administration/

16. intravenous drug administration/  
 17. enteric feeding/  
 18. parenteral drug administration/  
 19. exp infusion fluid/  
 20. rehydrat\*.tw.  
 21. (ORT or ORS).tw.  
 22. ((fluid or IV) adj3 therap\*).tw.  
 23. (water adj2 electrolyte adj2 balance).tw.  
 24. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 therap\*).tw.  
 25. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 infusion\*).tw.  
 26. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 drip\*).tw.  
 27. (nasogastric\* or (NG adj3 tube\*)).tw.

**28. or/13-27** [combination of index and text words for rehydration, oral or other] (765,497)

*Terms for Treatment with Antiemetics:*

29. exp antiemetic agent/  
 30. exp dopamine receptor blocking agent/  
 31. exp serotonin antagonist/  
 32. exp cholinergic receptor blocking agent/  
 33. exp antihistaminic agent/  
 34. exp benzodiazepine derivative/  
 35. exp corticosteroid/  
 36. exp cannabinoid/  
 37. (antiemetic\* or anti-emetic\*).tw.  
 38. anti-vomit\*.tw.  
 39. ((dopamine or serotonin or cholinergic or histamine) adj1 antagonist\*).tw.  
 40. benzodiazepine\*.tw.  
 41. "adrenal cortex hormone\*".tw.  
 42. cannabinoid\*.tw.  
 43. ("5-HT3" or "5-hydroxytryptamine").tw.

**44. or/29-43** [combination of Index and text words for antiemetics] (1,083,603)

*Terms for Treatment with Probiotics:*

45. probiotic agent/  
 46. exp lactobacillaceae/  
 47. exp Streptococcaceae/  
 48. exp enterococcaceae/  
 49. exp Saccharomyces/  
 50. Probiotic\*.tw.  
 51. Lactobacill\*.tw.  
 52. Lactococc\*.tw.  
 53. Enterococc\*.tw.  
 54. Streptococc\*.tw.  
 55. Saccharomyc\*.tw.  
 56. bifidobacter\*.tw.  
 57. (microbi\* adj3 supplement\*).tw.  
 58. ("L. GG" or "L.GG").tw.

**59. or/45-58** [combination of index and text words for probiotics] (246,321)

**60. or/28,44,59** [combination of treatments of interest: ORT, antiemetics, probiotics] (1,932,085)

**61. and/12,60** [combination of gastro terms + treatments of interest] (82,239)

*Terms for Child (≤ 18 years) Population:*

62. exp child/  
 63. exp pediatrics/  
 64. exp adolescent/  
 65. (infant\* or child\* or adolescen\* or teen\* or youth\* or young or p?ediatric\* or juvenile\*).tw.

**66. or/62-65** [combination of index and text terms for children] (2,865,771)

**67. and/61,66** [combination of gastro terms + treatment terms + child terms] (17,939)

Filter for SRs:

68. meta-analys\*.tw.

69. search\*.tw.

70. review.pt.

**71. or/68-70** [SR filter for Embase; J Clin Epidemiol 2007;60(1):29-33] (2,016,183)

**72. and/67,71** [combination of results + SR filter] (3,115)

73. limit 72 to human

74. limit 73 to yr="2000 -Current" (2,314)

75. remove duplicates from 74 (2,266)

**Database:** Global Health via Ovid <1910 to March 2012>

**Search Title:** Gastroenteritis KT Grant 4.0—SRs Only | Global Health—April 18, 2012—AM

**Date Searched:** April 18, 2012 (initial); May 2, 2012 (final)

**Results:** 253

*Terms for Gastroenteritis:*

1. gastroenteritis/
2. gastritis/
3. exp rotavirus/
4. exp norovirus/
5. vomiting/
6. dehydration/
7. diarrhoea/
8. gastroenterit\*.tw.
9. (diarrhea or diarrhoea).tw.
10. vomit\*.tw.
11. dehydrat\*.tw.
12. gastritis.tw.

**13. or/1-12** [combination of index and text words for gastroenteritis] (68,867)

*Terms for Oral, IV, and Nasogastric Rehydration:*

14. fluid therapy/
15. exp rehydration/
16. oral rehydration solutions/
17. oral administration/
18. intravenous injection/
19. enteral feeding/
20. parenteral administration/
21. parenteral feeding/
22. total parenteral nutrition/
23. rehydrat\*.tw.
24. (ORT or ORS).tw.
25. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 therap\*).tw.
26. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 infusion\*).tw.
27. ((fluid\* or IV or intravenous or enteral or parenteral) adj3 drip\*).tw.
28. (water adj2 electrolyte adj2 balance).tw.
29. (nasogastric\* or (NG adj3 tube\*)).tw.

**30. or/14-29** [combination of index and text word terms for rehydration, oral or other] (44,671)

*Terms for Treatment with Antiemetics:*

31. exp antiemetics/
32. exp antagonists/
33. exp benzodiazepines/
34. exp adrenal cortex hormones/
35. cannabinoids/

36. (antiemetic\* or anti-emetic\*).tw.

37. anti-vomit\*.tw.

38. ((dopamine or serotonin or cholinergic or histamine) adj3 antagonist\*).tw.

39. benzodiazepine\*.tw.

40. "adrenal cortex hormone\*".tw.

41. cannabinoid\*.tw.

42. ("5-HT3" or "5-hydroxytryptamine").tw.

**43. or/31-42** [combination of index and text terms for antiemetics] (13,871)

*Terms for Treatment with Probiotics:*

44. probiotics/
45. exp lactobacillaceae/
46. exp enterococcaceae/
47. exp streptococcaceae/
48. exp saccharomyces/
49. Probiotic\*.tw.
50. Lactobacill\*.tw.
51. Lactococc\*.tw.
52. Enterococc\*.tw.
53. Streptococc\*.tw.
54. Saccharomyc\*.tw.
55. bifidobacter\*.tw.
56. (microbi\* adj3 supplement\*).tw.
57. ("L. GG" or "L.GG").tw.

**58. or/44-57** [combination of index and text terms for probiotics] (74,734)

**59. or/30,43,58** [combination of treatments of interest: ORT, antiemetics, probiotics] (131,390)

**60. and/13,59** [combination of gastro terms + treatment terms] (7,314)

*Terms for Child (≤ 18 years) Population:*

61. exp children/
62. exp infants/
63. paediatrics/
64. adolescents/
65. young adults/
66. youth/
67. (infant\* or child\* or adolescen\* or teen\* or youth\* or young or p?ediatric\* or juvenile\*).tw.

**68. or/61-67** [combination of child terms] (392,814)

**69. and/60,68** [combination of gastro + treatment + child terms] (3,079)

Filter for SRs:

70. meta analys\*.mp.

71. review\*.mp.

72. search\*.mp.

**73. or/70-72** [filter for SR; not a validated SD filter, copied from Medline/Embase strategy] (248,854)

**74. and/69,73** [combination of gastro + treatment + child + SR filter] (491)

75. limit 74 to yr="2000 -Current" (253)

**Database:** PubMed via National Library of Medicine <last 180 days>

**Search Title:** Gastroenteritis

**Search Date:** April 19, 2012 (initial); May 2, 2012 (final)

*Results:* 8

((((((meta analysis[MeSH Terms]) OR meta analysis[Publication Type]) OR meta analysis[Title/Abstract]) OR review[Publication Type]) OR search\*[Title/Abstract])) AND (((((((child[MeSH Terms]) OR infant[MeSH Terms]) OR pediatrics[MeSH Terms]) OR adolescent[MeSH Terms]) OR minors[MeSH Terms])) OR (((((((infant[Title/Abstract]) OR child\*[Title/Abstract]) OR adolescen\*[Title/Abstract]) OR teen\*[Title/Abstract]) OR youth\*[Title/Abstract]) OR young[Title/Abstract]) OR pediatric\*[Title/Abstract]) OR paediatric\*[Title/Abstract]) OR juvenile\*[Title/Abstract])) AND (((((((probiotics[MeSH Terms]) OR lactobacillaceae[MeSH Terms]) OR enterococcaceae[MeSH Terms]) OR streptococcaceae[MeSH Terms]) OR saccharomyces[MeSH Terms]) OR lactococcus[MeSH Terms])) OR (((((((antiemetics[MeSH Terms]) OR dopamine antagonists[MeSH Terms]) OR serotonin antagonists[MeSH Terms]) OR cholinergic antagonists[MeSH Terms]) OR histamine antagonists[MeSH Terms]) OR benzodiazepines[MeSH Terms]) OR adrenal cortex hormones[MeSH Terms]) OR cannabinoids[MeSH Terms])) OR (((((((fluid therapy[MeSH Terms]) OR rehydration solutions[MeSH Terms]) OR administration, oral[MeSH Terms]) OR infusions, intravenous[MeSH Terms]) OR enteral nutrition[MeSH Terms]) OR infusions, parenteral[MeSH Terms]) OR parenteral nutrition[MeSH Terms]) OR parenteral nutrition solutions[MeSH Terms])) OR (((((((rehydrat\*[Title/Abstract]) OR ORT[Title/Abstract]) OR ORS[Title/Abstract]) OR water electrolyte balance[Title/Abstract]) OR nasogastric\*[Title/Abstract]) OR NG tube\*[Title/Abstract])) AND (((((((gastroenteritis[MeSH Terms]) OR rotavirus[MeSH Terms]) OR rotavirus infections[MeSH Terms]) OR norovirus[MeSH Terms]) OR diarrhea[MeSH Terms]) OR vomiting[MeSH Terms]) OR dehydration[MeSH Terms])) OR (((((((gastroenteritis[Title/Abstract]) OR diarrhea[Title/Abstract]) OR diarrhoea[Title/Abstract]) OR vomit[Title/Abstract]) OR dehydrat\*[Title/Abstract]) OR gastritis[Title/Abstract]))))

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